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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

MAY, 1929

## ORIGINAL ARTICLES.

### THE PROBLEM OF PIGMENT FORMATION.*

By Bruno Bloch, M.D.,

PROFESSOR OF DERMATOLOGY AND VENEREAL DISEASES AT THE UNIVERSITY OF ZURICH, ZURICH, SWITZERLAND.

As the subject of my lecture this evening I have chosen the problem of pigment formation, which I believe to be not only of dermatologic but of general interest. The particular pigment of which I wish to speak is called melanin and is an organic dye, which is found in all animals, from the lowest to the highest.

Pigment, its formation and function, plays an important rôle in every branch of biologic science. As a matter of fact, we encounter this problem in comparative zoölogy, biology, biochemistry, anthropology, physiology and pathology, and above all in dermatology.

I need only to remind you of the importance of the color of the skin and hair in the classification of the human races and its importance in human pathology, particularly in various endocrine changes, as, for instance Graves' disease, Addison's disease, pregnancy and scleroderma. Moreover, I wish to remind you that the most malignant growths are melanotic tumors, and that both the diagnosis and therapy of this condition are impossible without an exact consideration of the pigmentary changes.

The entire problem of pigment formation is extremely difficult and complicated and far from its complete solution. It is a morphological as well as a chemical problem, and no one who does not master both these factors can hope to approach it with success. It has, moreover, an entirely different aspect in the cold-blooded animals than in the higher ones. This difference lies in the morphology, the genesis and especially in the function of the pigment.

* Read before the Harvard Medical School, April, 1928.

Here it has a vital importance in temperature regulation, in mimicry and protective coloring, and the pigment cells themselves are provided with nerves and are capable of contraction and expansion. These faculties have degenerated to a great degree in higher animals. In these latter we can no longer speak of a vital function of pigment.

Before discussing the main problem I must give a definition of certain terms. We call *melanoblasts those cells which are capable of forming pigment, while those which contain pigment which they themselves have not elaborated, but have only obtained elsewhere* (*absorbed or phagocytized*) are called *chromatophores or melanophores.*

**The Distribution and Localization of Melanin in Higher Animals.** If we do not take into consideration the unimportant occurrence of melanin in certain parts of the nervous system, the melanin in higher animals is found only in two organs, which could, therefore, be designated "pigment organs." These are the eye and the skin.

In the eye we find pigment in the pigment layer of the retina. This pigment is ectodermal in origin. On the other hand, the pigment in the ciliary body and the choroid is of mesodermal origin. We have, therefore, in this organ ectodermal and mesodermal melanoblasts.

The human skin contains pigment in its ectodermal and mesodermal parts.

The ectodermal pigment of the skin and also of the mucous membranes is found in the epidermis (or epithelium), particularly in the basal cells, in the hair matrix and in the cells of the pigmented nævi, which develop through a metaplastic process from the epidermal cells.

All these cells form the pigment that they contain in their protoplasm; they are, therefore, melanoblasts of ectodermal origin.

The mesodermal part of the skin, the corium, contains in man and in certain higher mammals two entirely different kinds of pigmented cells.

One type is found regularly but in very varying numbers in the papillæ and also in the deeper layers. They are plump, sometimes somewhat branched cells of very variable form containing coarse granules of pigment. These are the chromatophores of the human cutis. As my assistant, Miescher, and I have shown, they do not form their pigment themselves. They are connective-tissue cells which have phagocytized pigment, which was originally formed in the epidermis. In some pathologic hyperpigmentations of the skin these chromatophores play a definite rôle, as, for instance, in tar, arsenic and Roentgen ray melanoses and so forth.

My collaborator, Sulzberger, recently described a previously unknown pathologic condition, in which there were curiously shaped, widely disseminated pigmented spots on the skin, which histologically consisted merely of very large heaps of such chromatophores (*incontinentia pigmenti*).

Another type of pigmented cells found in the cutis differs entirely in form, localization and nature from the above-described chromatophores. They are mesodermal melanoblasts, which I named *Mongolen-Zellen*. These cells lie for the greater part deep in the corium and are generally long and ribbon-like; they elaborate their own pigment, entirely independently of the epidermal pigmentation and embryologically long before this latter has appeared.

In certain animals this type of pigment is of much greater importance than the epidermal pigmentary system. For example, in the Japanese negro fowl these cells permeate not only the entire connective tissue, but also the internal organs, the ovaries and even the heart.

If you look at certain monkeys (macacus) you will see that some parts of the skin are colored a bluish gray. This color is also due to the presence of these mesodermal melanoblasts, which lie in the depths and shine through the transparent and unpigmented epidermis.

Analogous spots with the same color are found in all Japanese or Mongolian newly born, particularly in the sacral region. Attention was first called to this fact by the German, Baelz, and interpreted as pointing to a closer relationship of the Mongolian race to the apes. This worried the proud Japanese race, and there was great rejoicing in Japan when somewhat over twenty-five years ago the Japanese, Fujisawa, succeeded in the Munich Policlinic in demonstrating for the first time such a Mongolian spot in an infant of European origin. Since this time we have learned that such Mongolian spots can and do occur in the newly born of all races, but investigation with dopa and silver reactions first showed me that the microscopic elements, which constitute that which is macroscopically the Mongolian spot, are present in each and every embryo and newly born infant. We must, therefore, admit that the Japanese were right, insofar as the differences in the races are only quantitative ones. The occurrence of these cells seems to me to be one of the best proofs of the descent of man from the ape, or a common ancestor.

There is a second condition in which mesodermal melanoblasts are found in human beings. This is in the so-called blue nævi, which were first described by Jadassohn. These are large or small circumscribed moles, which differ from ordinary brown moles in their blue color. Microscopically they consist mainly of pigment cells, which are identical in every respect with the cells of Mongolian spots. Their blue color is caused by the same physical phenomena.

I once examined a number of Hindus and found numerous blue nævi. An extremely exceptional case is represented by this wax model. It is the case of a Swiss child, whose skin presented no less than 42 blue nævi, besides several brown ones.

As the cells of these blue nævi are mesodermal melanoblasts, the malignant growths which originate from these moles are, therefore,

true melanosarcomas. Such tumors were described for the first time by Darier. When one calls the melanotic tumors which originate from the ordinary brown nævi, melanosarcomas, as is so frequently done, it is an error from the viewpoint of their genesis. These, as I have shown, originate from ectodermal melanoblasts and are, therefore, *melanocarcinomas*.

**The Characteristics and Composition of Melanin.** In the foregoing, I have outlined the occurrence and distribution of pigmented cells. I come now to the most essential part of our problem, and the following points now interest us: Where is this brown dye formed? What is the mechanism of its formation? From what mother substance (melanogens) is it elaborated? What is its constitution and what is its significance and function under normal and pathologic conditions?

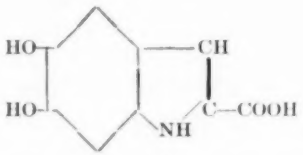
Lack of time only permits me to discuss briefly the above questions.

At first glance the method of determining the characteristics and composition of *melanin* seems simple and self-evident. It appears only necessary to extract the melanin from the organs, which contain it in great quantities (hair, skin, eyes) and to isolate and analyze it. This method has been tried a great number of times and has never led to satisfactory results. Upon closer inspection, the reasons for this are clear. It is absolutely impossible to isolate an organic substance which is so complicated and which cannot be crystallized, from the even more complicated milieu, represented by the pigmented tissues.

The data given by the different authors, among whom are many well-known biochemists, differ so greatly that they clearly demonstrate the fallibility of the method. These difficulties of the classical chemical method are shown by the fact that even the results of the analysis of melanins which have been artificially elaborated from known definite substances, such as tyrosin or dioxyphenylalanin, vary greatly. We find, for instance, that the nitrogen content varies from 4.3 to 8.5 per cent. But in spite of these facts, the investigations have given some information and I will, therefore, summarize the results, which seem to me the most important:

Melanin is an organic high-molecular dyestuff or pigment. It is amorphous, even upon Roentgen spectroscopic examination. It is insoluble in water and in organic solvents; it is a negative colloid, going into colloid dispersion in alkaline media. Natural melanin surely contains carbon, nitrogen, hydrogen and oxygen. The iron and, according to recent investigations by Dr. Schaaf from my laboratory, also the sulphur which have been found are impurities coming from the organs from which the melanin has been extracted (keratin). Schaaf and I have shown that the nitrogen is not amino nitrogen (not demonstrable by Van Slyke). According to Raper, the nitrogen in tyrosin melanin, which is formed artificially by the

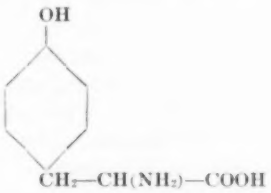
action of tyrosinase on tyrosin, is in an indol ring. As a matter of fact, under those experimental conditions he could isolate a 5-6 dihydroxyindol-2-carboxylic acid:




This fact explains why the melanin gives the pyrrol reaction. All melanins are capable of reducing certain metallic salts, particularly silver nitrate. This silver reaction is of great value because it enables us to make visible the smallest traces of melanins and perhaps even certain premelanins in sections of pigmented tissues.

**The Formation of Melanin by the Action of Oxydizing Ferments.** Since the ordinary chemical methods did not lead to satisfactory results, the problem had to be approached from a different angle, which we define as the biochemical instead of the purely chemical viewpoint.

Various authors, particularly Bertrand and Chodat, showed quite some time ago that certain plants possess oxidizing ferments capable of producing melanins from colorless organic cyclic complexes—melanogens—as, for instance, phenol, pyrogallol and tyrosin. Among these ferments, tyrosinase is particularly important. It is found in potatoes, mushrooms and other vegetable tissues. This ferment is specific and elaborates a melanin from tyrosin.



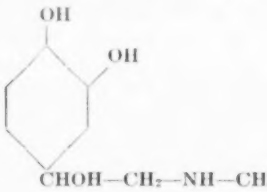

The chemical process of the formation of tyrosin melanin has been carefully studied by different authors, but Raper's recent work was the first to throw more light on the question. He showed that in the formation of tyrosin melanin dioxyphenylalanin was formed as the first intermediate product. Further products were the above-mentioned indol bodies.

Fürth was the first to conceive the idea that the formation of animal melanin also may be the result of a similar process. Even prior to this Biedermann found tyrosinase in meal worms. Fürth found tyrosinase in the hemolymph of butterflies, Pzribram in the ink glands of cephalopods and in the integument of certain cold-blooded animals.

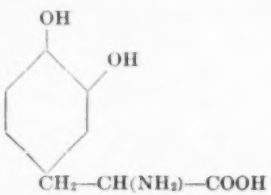
My own investigations have led me to believe that in higher

animals, particularly in mammals and man, the melanin is formed by a special ferment, the dopa-oxydase.

**The Dopa Reaction and its Results (the Formation of Melanin by the Dopa-oxydase).** My investigations were originally based on Addison's disease. In this disease we can observe one of the strongest hyperpigmentations of the skin combined with a lesion of an organ whose main product is a pyrocatechin derivate, *adrenalin*.




For this reason I experimented with the cyclic amino acid which is most closely related to adrenalin, that is, 3–4 dioxyphenylalanin, which for the sake of convenience I call *dopa*.




**Technique.** Frozen sections are placed in a 1 per cent solution of dopa for about twenty-four hours at room temperature under the conditions which I have enumerated in my article in the handbuch, (see literature) the most important of which is the adjustment of the H-ion concentration. They are then mounted as usual.

**The Principle of the Method.** The pigment forming ferment, the so-called dopa-oxydase is capable of converting the colorless dopa to a dark insoluble melanin, the dopamelanin. All cells which contain this ferment are darkened by this dopamelanin, as soon as they are brought in contact with the dopa. This darkening is proportional to the quantity and activity of this ferment.

The dopa method has the great advantage of enabling us to study the exact site of pigment formation It enables us, for instance, to observe the form of the melanoblasts and to demonstrate that pigment is formed only in their protoplasma and not in the nucleus. It also permits us to distinguish melanoblasts from chromatophores.

I may add, moreover, that it is possible to demonstrate the oxydase in extracts of the pigmented skin of newborn rabbits.

**The Results of the Dopa Reaction.** Following are the results of a more general nature:

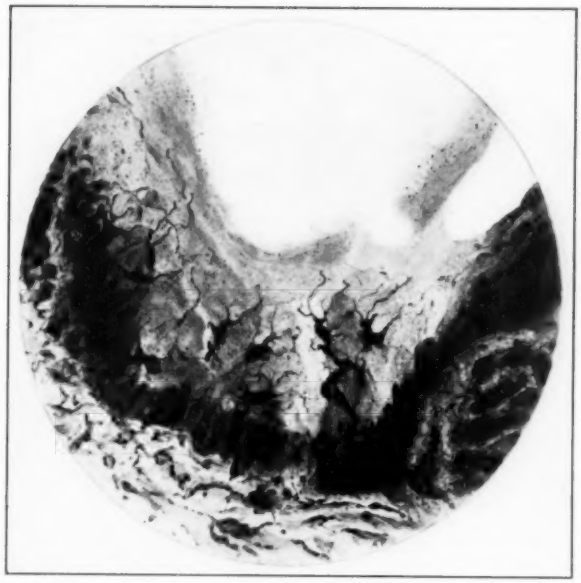


FIG. 1.—*Cells of Langerhans* (nerve elements) in the epidermis demonstrated through a gold method.

FIG. 2.—*Dopa reaction* in human skin ten days after application of *Thorium-X*. Transformation of basal into *Dendritic cells*.

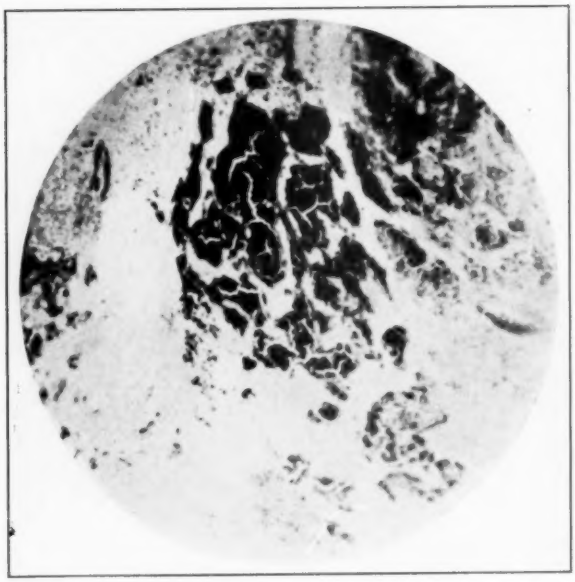


FIG. 3.—Dopa reaction in *Melanocarcinoma* originating in the skin.

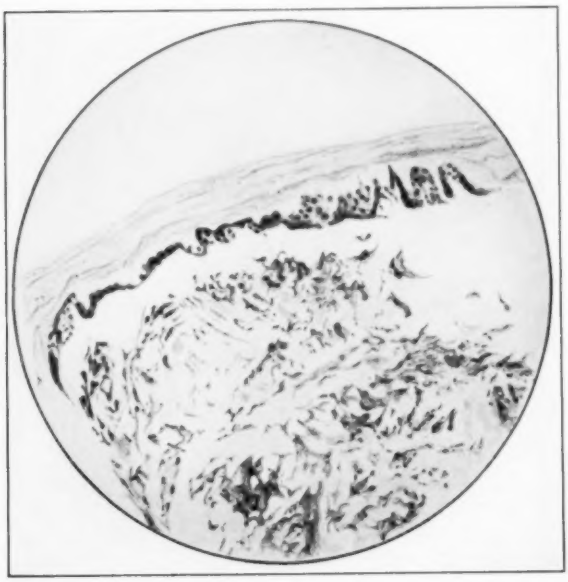


FIG. 4.—*Blue Nævus.* Dopa reaction. The reaction is positive in both basal cells of the pigmented epidermis as well as in the mesodermal melanoblasts (cells of blue nævus).

1. Under certain definite conditions, which I have given in detail in my work on this subject, the reaction is specific. No other substance, such as, for instance, pyrrol, tryptophan, not even tyrosin or adrenalin give the reaction. The slightest change in the dopa molecule is sufficient to make the reaction negative.

2. The reaction is of fermentative nature and satisfies the requirements necessary for such a supposition as I have shown in my experiments.

3. The reaction is only positive in the protoplasma—never in the nucleus. That is one of the strongest proofs against the theory that the nucleus takes part in the pigment formation.

4. *Dendritic Cells.* The dopa reaction, moreover, brings to light an extraordinarily interesting biologic phenomenon through a morphologic picture. It shows that melanoblasts very often possess numerous branching processes—hence the name dendritic cells. These curious dendritic cells have been known for many years, in lower as well as in higher animals. They can be observed under certain conditions in native sections and even better through the use of the silver method. Becker, of Chicago, in investigations undertaken in my clinic, has shown that they are more widely distributed than hitherto supposed, both in the human skin and in the mucous membranes of ectodermal origin.

But it was the dopa reaction which first showed how very frequently pigment-forming cells have this form and that there are cases in which practically each and every basal cell has dendrites. This was demonstrated, for instance, by my assistant, Peck, in studies of pigment formation in human epidermis after exposure to thorium-X.

The biologic significance and the genesis of these pigmented dendritic cells is a special problem in itself which until now has not been quite satisfactorily solved. In my opinion, they are melanoblasts in an active stage of pigment formation.

At any rate it is absolutely wrong to identify them with the Langerhans cells, as has been frequently done, for instance, by Pautrier and Masson. The true Langerhans cells which can be best demonstrated by gold methods have nothing to do with pigment formation. They are nervous elements, parts of the highly differentiated nervous system of the epidermis.

I think it would interest you to see some pictures of these elements which I have made by my modification of the gold method, in some as yet unpublished studies on this subject. This may give you an idea for the first time of what the nervous system in the epidermis really means. (Fig. 1.)

We will now undertake to answer the following important questions:

Where, when and under what conditions is the dopa reaction positive?

In all places in which we must assume that an autochthonic formation of pigment takes place the reaction is positive. It goes absolutely parallel with the formation of pigment in regard to time, place and intensity; there, where there has never been formation of pigment, or where this has ceased, the specific reaction is always negative.

**Some Concrete Examples of the Results Obtained with Dopa Reaction**

(*a*) *In the Eye.* As I have stated above, the pigment of the eye is formed early in the embryonic period, as well in the ectodermal retina as in the mesodermal choroidea. As was shown by my collaborator, Miescher, in a very painstaking and technically difficult investigation, the dopa reaction is positive in both and, which is more significant, exactly and only during the period of pigment formation (during the fetal life). Indeed, for instance, in the case of the chicken embryo, the pigment formation in the retina begins on the third day, reaches its maximum on the seventh and ceases on the eighteenth day. In the choroidea it begins only on the fifteenth day. Only at that particular time the dopa reaction is positive.

At first glance it may seem peculiar that pigment formation in the eye takes place only during a short time in the embryonic stage. When we consider the matter more closely, however, we see that this must be so on account of the function of the eye which would be impaired if the pigment formation was as easily influenced by outside factors, as is the case in the skin. As far as we know, there is only one condition in which the rule is broken. This occurs when malignant pigmented tumors (melanocarcinomas or melanosarcomas) arise from the pigmented parts of the eye. In this case the latent pigment function and parallel with it the positive dopa reaction reawaken.

(*b*) *In the Skin.* In the ectodermal parts of the skin and the mucous membranes the dopa reaction is positive in all cells which are capable of producing pigment, namely, in the cells of the basal layer of the epidermis and follicles and in the matrix of pigmented hairs. In all places one can here again observe the absolute parallelism between the first appearance of pigment granules on the one hand and the positive dopa reaction on the other. In the hair of the human embryo the first traces of pigment are found about the fourth to the fifth month. At this time and in the same places the first melanoblasts with positive dopa reaction are to be found. Only much later, at about the time of birth, do we see pigment formation concomitant with a positive dopa reaction in the basal layer of the epidermis, probably under the influence of light.

It is well known that graying of hair (canities) is a usual accompaniment of old age. The causes for this more or less physiologic fact have been investigated in vain by many scientists, among them the

great Metchnikoff. In the light of my theory, the process becomes clear. The matrix of the white hair does not give a dopa reaction. It has lost its pigment-forming oxidizing ferment, the dopa oxydase, with a resulting pigment-free or white hair.

If we make a section through the skin of a guinea pig, which is partly colored and partly white, the dopa reaction is positive only in the matrix of the colored hairs and always negative in the case of the white ones A similar fact is to be observed in the case of vitiligo in man; there where the skin has become definitely pigment-free, the reaction is negative, whereas in the surrounding skin the reaction is positive and often increased in the hyperpigmented ring.

One of the most effective causes of skin hyperpigmentation is, as is universally known, the exposure of the skin to rays such as ultra-violet, Roentgen rays, thorium-X, etc. Under no other conditions, do we find such strong dopa reactions and so many and such beautiful dendritic cells as in such rayed skin. In the microscopic demonstrations, I wish to draw your attention to the sections showing a dopa reaction in a skin which has been exposed to thorium-X.

The dopa reaction is furthermore positive in the cells of pigmented brown moles—just as it must be according to the theory—and naturally also positive in the malignant tumors which arise from them, the melanocarcinomas. This applies not only to the primary tumors, but even to far distant metastases.

As I have said in the first part of my lecture, in the mesodermal part of the skin, in the corion, we must distinguish two entirely different sorts of pigmented cells—the chromatophores, which are nothing but pigment phagocytizing connective-tissue cells, and the pigmented cells of the Mongolian spots, the blue nævus, etc., which elaborate their pigment themselves. If the theory is correct, the dopa reaction must be negative in the chromatophores and positive in the Mongolian cells. That this is so, you can plainly see from the histologic pictures which I am showing you.

The curious pigment cells of the Japanese negro fowl, the gray mouse, the apes, the Mongolian spots and the blue nævi, which we have learned to know, are, therefore, actually mesodermal melano-blasts, and tumors arising from the blue nævi are melanosarcomas.

I need scarcely remark that a tremendous number of other problems in this field are still awaiting solution.

Of these, I only want to touch on the one concerning the nature and origin of natural melanogens.

As I have emphasized, the dopa reaction is an indicator of the presence of the pigment-forming oxydase. But this fact does not necessarily mean that dopa is the actual mother substance of natural melanin. However, there are some indications which suggest that pyrocatechin derivatives may play a rôle as substrates in the formation of natural pigment. I have already mentioned two points: the specificity of the dopa reaction and the occurrence of

dioxyphenylalanine in formation of melanin by the tyrosinase-tyrosine reaction.

I want to draw your attention to a third and very interesting fact which is generally ignored. The only physiologic pyrocatechin derivative is, as far as we know, adrenalin. Under pathologic conditions, except in one particular case, pyrocatechin derivatives play no rôle. As Salkowsky, Tannhauser and I have found, such substances can occasionally be demonstrated in the urine of patients with general melanocarcinomatosis, melanemia and melanuria. This cannot be mere coincidence. It is logical to assume that these pyrocatechin derivatives come from the mother substances of melanin which must, of course, be formed in great amounts in such cases, become free through the disintegration of the tumor cells, get into the blood and are eliminated through the kidneys.

From all the facts, which I have now elucidated, I believe myself justified in drawing the following conclusion, which contains the gist of my researches on pigment formation by means of the method of the dopa reaction:

**Conclusion.** The specific dopa reaction is positive in higher vertebrates in all places where melanotic pigment is formed, that is, in the cells which are capable of producing pigment, the melanoblasts. A close parallelism exists between natural spontaneous pigment formation and the result of the reaction, as regards time, place and intensity. It is this parallelism which logically points to an innate connection beween both phenomena. Wherever the natural formation of pigment is going on, the reaction is positive, and where pigment formation is temporarily or definitely lacking, the reaction is negative. Thus the dopa reaction must be an indicator of the existence of the faculty of natural melanin production (however not of the presence of melanin itself).

The agent within the cells, which is responsible for the dopa reaction, has the characteristics of an oxidizing ferment. We conclude that this oxidizing ferment which is demonstrated by the specific dopa reaction, is identical with the natural pigment producing oxydase and therefore call the latter dopa oxydase.

The nature of the mother substances of natural melanins (melanogens) is not yet known exactly. However, certain facts may indicate that pyrocatechin derivatives play a rôle in the process of the formation of natural pigment.

I hope that I have been able to show in this short lecture that modern dermatology does not limit itself to a small field only but includes interesting biologic problems of great general importance.*

* For complete details as well as bibliography, I refer the reader to my publication: Das Pigment, Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Springer, 1927, vol. 1.

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# THE AGING OF THE HEART MUSCLE REGARDED FROM A GENERAL BIOLOGIC POINT OF VIEW.*

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**Introduction.** In any current discussion of the subject of diseases both in and of old age, an effort must be made to define accurately first what is meant by growth and second what is meant by disease. Without making this effort it is unlikely that satisfactory ideas of the nature of this matter can be attained. I think it is probable that an enquiry in this special form is new.[1] To physicians, the question assumed significance because of certain occurrences; it became apparent[2] several years ago that a time had arrived when great numbers of people were no longer dying of acute infectious diseases and that the days of those who were saved were being terminated by quite other processes. For this reason, the importance of the conditions in which old age is spent and the diseases to which it is subject appear to require more exact examination and analysis. The reflections which were entertained concerning the change were far from precise as can readily be appreciated now, when it is recalled that to meet the new issue Societies for the Prevention and Relief of Heart Disease were created. There can be little doubt that the nature of the problem with which these societies intended to deal was inadequately understood. It was known but, as Sir James Mackenzie would have said, it was not appreciated what were the varieties of the disease which were involved. This has been found a point of importance because, as is now known, susceptibility to given diseases varies with age. Nor was it known what number of individuals was afflicted by each one of them. There would, it seems certain, had these matters been clear, have been less emphasis on prevention and relief and more no doubt on reflection, on analysis and on investigation concerning what actually was the new situation.

**General Considerations.** In a sense, the subject I mean to discuss is not new. Speculation on the natural history of man, his origin, growth and destiny is so ancient, that it precedes even the systematic writings of Aristotle. But it is necessary first of all to become convinced that this subject involves considering both the state and the diseases in and of old age, and is, as I believe it should be, a matter of natural history. Clearly, beginning perhaps with the Psalmist, there has been a popular natural history. In recent years, a recru-

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descence of interest in precisely this matter has developed; many men have supposed that there was something arbitrary in the selection of the Biblical term of seventy years, that there was in all probability something that might be altered to prolong this gift of life, if not indefinitely, at least beyond the conventionally accepted term. Whether there is justification in this view is open to debate but better still to investigation. Confidence in the belief, that the duration of the accepted span was not so firmly fixed as was commonly believed, was stimulated by a number of occurrences. It was obvious that actuarial analysis was making it appear that expectancy at birth of the duration of life was undergoing change. In Massachusetts, after a lapse of fifteen years, life appeared to have lengthened 30 odd per cent. Elsewhere similar phenomena were observed. That this alteration was related to the gradual disappearance of infectious diseases in the earlier years was not at once apparent; nor did one appreciate the fact that expectation of life in the later decades had not increased. During these later years also the extraordinarily interesting demonstration by Carrel that tissues when explanted from metazoa could under appropriate conditions be maintained alive in subcultures indefinitely, just as could bacteria, yielded the impression that the gift of immortality had been bestowed on them, and came not only as a great surprise but led many speculators to infer that what is possible in their case might be possible also in that of the whole complex organism. But the step from these conceptions to those having in view an adequate, not to say complete, understanding of the life processes of man and of the accidents and diseases to which he is subject is great. What these processes actually are and how they may be described seems, and without doubt is, a long and tedious labor. But to be in possession of the knowledge which can be gained only in this way is in all probability essential, certainly to understand and in all likelihood to help in ameliorating the later life of man.

Even superficial reflection suggests that striking changes occur in the function of important organs. Consider for instance the stomach. At first it tolerates and digests foods that are especially adapted to it, simple perhaps; but later substances of greater complexity are managed safely; finally a return to the earlier situation apparently takes place. There is an evolution and an involution of structure and of function. That there are successive changes in the case of the long bones and of the skeletal muscles it requires a mere mention to appreciate.

I have said that this is an ancient subject. Growth, in the sense in which I am using the term, means successive changes in an organism both from the point of view of its bulk or mass which increases, as also from that of the progressive differentiation of all the tissues and organs of the body. Nor is the term confined to that stage in which bulk or mass continuously increases; growth continues also

during the period of involution, of decline, of old age. Growth now is negative where before it was positive. Parallel with change in bulk there is continuous differentiation in the intimate form and function of the organs and tissues, always in a forward direction, never backward to an earlier form—never as we say reversible. The idea should not be gained, however, that the rate of this change through life is uniform; on the contrary every effort to describe the whole of it in the form of a single curve equivalent to a single mathematical expression has met with failure. Brailsford Robertson,[3] among the more recent to make the attempt, was obliged in describing the curve of metabolic rate and the attending weight curve to divide the life span into three parts, infantile, juvenile and adolescent, each of which required separate description and equivalent mathematical expression encumbered with variables so complex that to understand the process simply becomes too difficult. Nor does the organism as a whole grow uniformly, sometimes it is this organ, the thymus gland for example, which exhibits accelerated growth—sometimes another.

**Theories of Senescence.** Murray and I[4] have recently been engaged in analyzing the various aspects from which speculation and research have been concerned with this subject. There have been essentially mechanistic and teleological theories. As a type of *mechanistic theory* may be taken Herbert Spencer's, that matter during growth (and evolution in general) passed from simple and homogeneous to complex and heterogeneous states. This change implied an integration of matter and the dissipation of motion. To show how this generalization became applicable in organisms, either unicellular or multicellular, the life of a single cell may be cited. In the protoplasm, solid particles were imagined to accumulate and to stiffen the substance; the walls became less permeable to the entrance of necessary, perhaps foreign matter; the electrical conductivity of the cell diminished. In the nucleus similar changes took place, except that here these transformations were even more conspicuous. As time went on, the pigment, the so-called metaplastic granules multiplied, and the excretion of substances elaborated in the cell became more difficult. When on this account the relation between intake and output of the cell became sufficiently unfavorable—the cell—the organism—died. Many suggestions have been made as to how, precisely, changes like this take place. So far no suggestions regarded generally as satisfactory have been adopted. The behavior of silicic acid, for instance, supplied an analogy. It is well known that this substance though a suspension when fresh, gels on standing. Birth represents a fluid state, a state of suspension; death an immobile one. This is the simplest of such notions. Other mechanistic theories involve the idea of control of the processes of growth by some substance manufactured, for instance, by one of the ductless glands, or by some tissue which

somehow develops relatively a more active metabolism and by so doing leads on the other tissues less favorably endowed. This is Child's[5] idea which has been tested by him in many interesting experiments and which he thinks represents the presence of metabolic gradients. There are other theories of this class, but these illustrations suffice to indicate the sort we have designated as mechanistic.

Instead of attempting to "explain" the phenomena of Nature, to use Hobson's phrase, *teleological forms* of statement have been employed. The behavior of an organism or of a system may be examined with the view to learning whether its mechanism tends to satisfy a purpose, of course not explicit. I might cite the second law of thermodynamics as an example of such a theory, which states that all energy tends toward a minimum. Aristotle suggested a crude statement of the law when he supposed that in a newly born creature an amount of innate heat was implanted sufficient to carry it through life; in its course this was continuously dissipated. Death was the state which documented its complete disposal. Henderson's "Fitness of the Environment" is another example of this way of thought. It is the function of science and its methods according to theories of this sort to explore the justice of the view which is advocated. The difference between the two methods of viewing natural phenomena suggests for a teleologic one the possibility of adopting a direction for research. The theory presents the "Fragestellung." I need not recall other examples.

These being the theories, investigation has in practice been conducted with the view to ascertaining what *changes in form or matter*, that is to say in anatomy, and what changes in function, that is to say in physiology, may be detected. The construction of weight curves I have already mentioned. To describe successive structural changes at the beginning of life is the function of embryology. But after this early period when the rate of change becomes slower, there has been less interest in describing body and organ and tissue growth. To microscopic changes, more attention has, however, been paid. I recall measurements of the nucleoplasmic ratio which Minot[6] thought decreased with time but with which Hertwig[7] later disagreed. The difficulty of ascertaining this relation has led others as Le Breton and Schaeffer[8] to attempt to estimate it chemically as purin and nonpurin substances.

Chemical differentiation may be regarded as an ultimate form of anatomic structure. Research in the direction of defining constitution in this way has also been attempted. Desiccation, or decrease in the concentration of water, is, for example, one of the commonest observations in the aged, having as a consequence increase in the concentration of nitrogen. In certain animals, the concentration of hydrogen ions in the plasma (as in guinea pigs) and in the blood (as in chicken embryos) has been studied and is now known to alter, as is likewise in man the tolerance to sugar and its concentration in

the blood. There can be no doubt, therefore, that the body undergoes both structural and chemical changes.

Through life there are *changes in function* also. To measure certain of them has been attempted in a variety of ways. Conklin,[9] and indeed most writers on the subject, has shown that with time there is slow decline in the metabolic rate; Osterhout,[10] that the permeability of membranes decreases; Child's[5] experiments indicate a decrease in susceptibility to anesthetics in simple organisms; Murphy[11] and others, that susceptibility to infection differs in succeeding periods, irrespective of the history of exposure. Clearly the body is subject to change; clearly also its changes can be described. If we are to know the body these changes must be systematically investigated. To possess this knowledge has important consequences both for hygiene and therapeutics.

**Factors which Modify the Process of Growth.** Concerning the influence of heredity and of infection in early years on the process of aging or on the duration of life something should be said. Certain *infectious diseases*, as measles, pneumonia, malaria and varicella, are not now regarded as having an influence on the natural normal growth of heart muscle. But others such as tonsillitis, rheumatic fever, diphtheria, typhoid and scarlet fevers are not without effect on the heart. It would be going too far perhaps to say of the latter group that the nature of the injury to which the heart is subjected is known precisely. Insofar as this is confined to the valves, the outcome need not be supposed to be different from that which is expected when these are affected by other diseases, though two types must be recognized—one a destructive process, the other a productive one. But when the muscle of the heart is also involved, the issue may be different. It is unnecessary to describe the initial lesions—the focal necroses in typhoid fever; the destruction and regeneration of muscle fibers in diphtheria; the lesion still unknown in pertussis but attended it seems, at least occasionally, by enlargement of the heart, about the end result of which there is still no exact information; the essential Aschoff body in rheumatic fever. How much the effect is one of destruction of muscle fibers, how much of genuine regeneration, whether fiber is replaced by fiber, or whether in the end there are fewer than before or whether more; whether the fibers or some of them are replaced by connective tissue which itself has an influence on the subsequent process; whether the sole ultimate effect is hypertrophy; whether inflammatory tissue survives as scars or later contracts so that it is no longer distinguishable from perivascular connective tissue—all these are matters about which it is desirable to have more precise knowledge as well as better defined ideas concerning the end result of the processes on the duration of the life history of the fibers which survive. It seems necessary to recollect that beside the structural manifestations which are easily perceived there may be others more subtle which in

the nature of toxins or other poisons have had their origin in the original diseases and which having once influenced the behavior, perhaps minute and chemical of the muscle, thereafter continue to affect subsequent development in a manner the ultimate result of which is still unknown. This is the sort of effect about which no more than speculation may be indulged. Of one thing only is it possible to be certain; if actuarial experience persists in finding that normal expectancy is altered when one of these diseases has been a factor, the search for the condition underlying this result must be intensified. More for the moment cannot be said.

The influence of *heredity* is a different matter; the evidence here so far is in no sense anatomic—at least so far as the heart muscle is concerned, but rather statistical. There is, of course, the popular natural history which refers to the arteries. But about this there seems now to be doubt; Pearl thinks that even beyond the state of these, the degree of longevity of one's ancestors plays a determining part, though on this point there is also dissent. The matter of the arteries—about the heart muscle itself there are no criteria—brings up for discussion the difference between age expressed in numbers of years lived or chronologic age and age manifested by physical states or physiologic age. The meaning of the difference is simply that a man may be older, or younger, so far as his physiologic state, which implies the number of years he is likely still to live is concerned than the number of his years, his chronologic age, would have led one to suppose. Interesting as is this distinction, and important when it is better understood, now it is practically impossible to appreciate in terms of structure and of course of correlated function how either acceleration or retardation in the life process may have taken place. Nor is it as yet possible to be certain whether any environmental influence may have had a share in the process—such as the more exacting nature of modern life in the way either of greater speed of motion, greater competition in the economics of living, greater complexity in the arrangements of existence. Many a captain of industry, many a legal luminary, many a professor of classics, still lives out his allotted days.

Indulgence in athletics, such as rowing, football, baseball and track, seems to exert an influence on longevity as Dublin has recently shown in an unfavorable sense—but whether this influence is constant and to what mechanism it is due, it is not yet possible to be certain. The effect of overexertion on the heart and on the hypertrophy of its fibers and the probability that muscle once in this altered state survives a shorter period of time than when the processes of life are permitted to proceed at a customary natural tempo must be studied in this connection. Primarily the method of the investigation must be statistical; later the facts may become expressible in physiologic or chemical terms.

**Classification.** The study of man will I believe go forward best when it is related to the main stream of biologic thought. Against this background, it becomes easier to understand what variety of phenomena must be investigated in order to understand better the diseases, so-called, of old age. It is necessary first to enquire what are the phenomena of old age. Is every complaint, is every deviation from a preconceived normal, of the senescent organism to be regarded as disease? Are certain disorders to be anticipated, natural and inevitable, or, are there not also those which need not be anticipated, which are unnatural and are perhaps preventable? Do these two groups form distinguishable classes?

It is not my intention to make a comprehensive definition of disease, but rather to indicate that if the term disease is retained to designate all the ills to which the flesh is heir, there may be profit in attempting to distribute the phenomena under headings which describe more nearly how they came into being—whether, for example, as accidents such as infections or as accidents dependent on growth.

Consideration of the nature of growth suggests the probability that as part of it, may be reckoned occurrences which are now classified as diseases. If they are not diseases, a restatement is required of the definition of disease. The term disease then becomes applicable to phenomena which, from the point of view of growth, that is to say of the aging process, are not or need not be anticipated, are unnatural, or are preventable. If this distinction is just, it becomes necessary obviously to class certain occurrences as disease and others as phenomena of growth or of progressive differentiation. The extent to which this classification is possible or practicable depends on the amount of knowledge of the nature of the aging process which is from time to time available. This knowledge is still so slight that transference from one to the other class, from growth to disease, of many phenomena must necessarily take place until their nature is satisfactorily defined. But the establishment of classes is important here, as always in science. This is a matter not merely of words. The designations may be chosen differently. The term disease may be taken to include both classes—that which involves the processes of growth and that which accounts for the accidents of existence. There is, moreover, a practical need for this method of thought and procedure. Prognosis and therapeutics depend upon it. A process which is preventable or curable invites a different order of attention to its study and relief, from one which, like the progress of life itself, renders effort with such an object both aimless and futile.

**The Growth in the Heart and Circulation.** I have thought it proper to preface these remarks to what I intend to say on the subject of the heart muscle in old age, first because I am unaware that this aspect of the matter is often the subject of current thought and description

and second, because it serves to illuminate this subject which lies peculiarly in its province. With improvement in hygiene, more and more people come into the position of realizing their natural and allotted span of years. For this reason, the structures which appear to bear the brunt of the stress of life are the heart and the bloodvessels. I say "appear to bear this brunt" because medicine and physiology, being still youthful sciences, find it useful and easier to think in mechanical terms. It is not that other organs and tissues are not also exposed to wear and tear, but that the mechanical stress of the heart and circulation is obvious.

In the circulation, the question as to how aging progresses from the point of view of *function* has been investigated in a number of directions. It is known, for example, through the careful study of Faber and James,[12] of Alvarez[13] and of Burlage[14] that curves descriptive of systematic changes in the blood pressure may be drawn. Before the publication of these investigations, data less refined than theirs were already available. There is still an impression, however, that further study, still more careful selection and precise management of the material is required. Then, Gilbert[15] has discovered a change in the degree of inhibition which the vagus nerves on being pressed exercise in the degree of their control of the rate of the heart; Crawford[16] studied a related phenomenon by injecting atropin and observed the effect on the heart of releasing it from vagus control. Both found that their result could be stated in terms of age.

That the bloodvessels undergo change is another of the observations of daily life. Do we not say "A man is as old as his arteries?" Friberger[17] and later Bramwell[18] have studied this matter in an interesting and ingenious manner. It is well known that a fluid of a certain consistency flows at a rate through a vessel, depending on the elasticity of its walls. Bramwell found that at the age of five years, blood flows at the rate of 5.2 meters per second; as the vessels stiffen with years, the rate rises conspicuously so that at eighty it has mounted to 8.55 meters. The increase is striking—from 5.2 to 8.55 meters per second. A corollary that might have been expected because of stiffening of the vessels, is the observation by Daly[19] that the arterial system of young animals can accommodate more blood relatively speaking than that of older ones, a function which he called the "potential capacity increment." These and similar researches may readily be believed to form the bases of new and important concepts of the behavior of the circulation.

In the heart, phenomena of growth and change are also encountered in its *form* and *structure*. The heart grows. It changes its form during the embryonic period. A simple tube becomes a complex system of cavities. The orifices which accommodated the fetal circulation change conspicuously; the organ becomes adapted

to the circumstance of aërial respiration. The wall of the right ventricle which was at first thick later becomes thin relative to that of the left ventricle. These matters of form having become adjusted at birth, increase in size continues to take place. Just what the course of this is, is known tentatively.

Whether or not the size of a heart is normal, is one of the most important matters for the clinic to be able to ascertain. The simplest data are those obtained by weighing postmortem. Tables expressing this information are available, but they are scarcely satisfactory. What is natural for a given race, constitution, age, height and weight needs careful separation from measurements obtained in cases where these factors are either unknown or disregarded; or where the effect of disease, no matter what its nature, has been permitted to influence the computation. Were these data all given their due importance, it would be possible ultimately to be in possession of tables accurately descriptive of each of the relations which we require to know. The heart of a Japanese of a given age and height may obviously yield a different figure from that of a north German. Were the facts known it would be possible to state that the weight curve of hearts bears a definite relation to that of their proper bodies and that these curves describe certain characteristic changes with time. In a given case, a deviation from the natural state could then easily be ascertained.

To weigh the heart postmortem is then the simplest way of learning its absolute and relative dimensions. But in the clinic we are driven to substitute methods of measurement. Percussion now practised about one hundred years, since its introduction by Auenbrugger and later by Corvisart and modified in many directions since, is the earliest of the methods. Before 1800 the clinic was without methods. Since 1893, the use of the Roentgen ray has become a valuable adjunct to the earlier techniques. Use of the general structure of the individual is made by relating the diameter of the heart to that of the chest. But to estimate the relative dimensions of the various chambers of the heart, these methods are inadequate. To be adequate requires possessing all the data mentioned in the case of weighing but in addition, knowledge of the shape of the heart and its position in the chest, two factors often mutually dependent. I refer to the so-called vertical, pendulous, or hanging heart, in contrast to that which maintains a transverse position. Whether a given heart is enlarged depends furthermore on its initial position and size. A vertical heart, the subject of mitral stenosis may increase greatly and may yet fail to extend as far as the left midclavicular line. It may in fact appear smaller than a heart of normal size which lies in a horizontal position.

It is necessary in practice to ask, What should be the size of *this* heart—is this one enlarged? This question is the beginning of the

analysis of the state of the heart. To answer it, it is necessary to draw on knowledge of the natural history of man—which is unfortunately still meager.

Manifestations of growth are conspicuous also in the *muscular apparatus* of the heart when this is examined histologically. At the very beginning of its beating, there is doubt whether any structure characteristic of the later fully developed contractile element is present. There is fair agreement that at first individual cells exist. Later these, by some method, how is not yet clear, become modified and coalesce so that the well-known syncytium comes into existence. How the bulk of the heart increases, despite the numerous researches which have been devoted to this end and the many theories which have been proposed is not yet known, either in the longitudinal or in the transverse direction. After birth histologic changes do not cease to take place. Longitudinal striations and transverse discs occur early, but intercalated discs make their first appearance at birth and increase in number and complexity throughout life. But about the nature and meaning of these there is no knowledge. Pigment begins to form about the tenth year and is deposited in a bipolar fashion about the nuclei. The amount of this increases progressively until in the sixth or seventh decade it lends to the appearance of the muscle a brown color. It is known as brown atrophy to pathologic anatomists, but there seems little doubt that its occurrence is a natural, normal phenomenon. The nuclei themselves undergo change, becoming larger, more irregular and on cross section seem to present grooves along their long axes. All is in a state of continuous change. An additional word should be said about transverse discs. During the period when the muscle is taking on a brown appearance, these also change. Their height becomes progressively smaller, so that in later life they seem compressed. This appearance together with the increasing number and complexity of the intercalated discs is so characteristic as to render it possible to distinguish microscopically old from young muscle.

As to the meaning of all these changes for function, little can be said aside from recalling that general knowledge, which is awareness of the fact that with advance in years comes decrease in bodily vigor and strength. But what is responsible for the change is less difficult, within very circumscribed limits, to define. Water, certainly, is one of the important constituents of the body; there is little doubt that its concentration suffers a conspicuous reduction in the case of most elderly individuals. It is probable that heart muscle takes part in this general process of desiccation and that it is this which is responsible for the change.

Just as the muscle is complex in structure, so must it be supposed that its *chemical structure*, its "Bausteine," is complex. Beside water, there is glycogen, and fat, especially of the double refracting variety and the protein substrate. Undoubtedly all these undergo

important alterations though no beginning has been made in describing them. The total result is, however, apparent; the muscle of the aged is a different muscle from any that preceded it.

It is necessary now to discuss the importance of hearts obviously larger and obviously smaller than a general established average, those which have become *hypertrophic* or *atrophic*. Karsner, Saphir and Todd[20] tell us what changes the muscle fibers have undergone in hypertrophic hearts. Here there is no change in the number of units but an increase in the diameter of the individual fibers. In atrophic hearts, on the other hand, there occurs a genuine reduction in the number of units. Of especial interest are the results in atrophic hearts. That these exhibit actual diminution in the number of fibers has consequences which are important in developing ideas concerning the history of the muscle. An understanding of the circumstances is important in which heart muscle, when put to strain, can hypertrophy and also when, under other circumstances, it can regenerate. And it is also important to learn whether and how far these functions are changes dependent on age.

Concerning the history of change in the *bloodvessels* of the heart, it is necessary to possess intimate knowledge: so much of the life of the muscle depends on them. Gross[21] by means of injection preparations has made signal contributions to this subject. At birth the number of vessels, relative to the left, is somewhat in excess in the walls of the right ventricle. Later, the situation is reversed. After the fifth or sixth decades, there is another change; the relative differences become more significant but the absolute ones, striking; in the walls of both ventricles there are relatively fewer vessels, sometimes so few as to awaken wonder that there can still exist a sufficient blood supply. The mechanism which underlies this appearance it is important to examine. Does it depend on involution of the vasa vasorum, as Winternitz[22] thinks in certain definite connections, and so on down to the very capillaries, or is it a process primary in the intima or media? It is a mechanism about which there is as yet inadequate knowledge but one without doubt which is important in understanding the general process which transforms the heart as a whole.

I come now to consider the meaning of all that I have been saying in the attempt to comprehend the diseases so-called of the heart in old age. Aschoff and Tawara,[23] in 1906, declared that for weakness of the heart muscle, for heart failure, they could find no histologic equivalent. One wonders whether this generalization would be adopted if it were made to include the considerations I have been urging. Aschoff and Tawara were thinking of sudden death, especially in connection with infectious diseases—I, of the gradual differentiation of the body. It is of course necessary to weigh the possibility of the occurrence of acute heart failure at all ages since naturally it may take place also in old age. But that is another

matter from the object of present interest from studying the association of progressing weakness, of progressing failure, with progressive decay.

**Clinical Manifestations of the Senile Heart.** Beside changes in the proper muscle fibers, in the bloodvessels, and in the constituent tissues, two additional sorts may be recognized; first collections of cells which are foreign to the heart and which are usually associated with the concept "*inflammation*," and second, the bundles and *masses of connective tissue* which are found either separating muscle fibers or so disposed that muscle fibers are found among them. That such tissue occurs after infectious diseases is, of course, well understood. These events are usual in youth. But in older people, apart from an association with the process of infection it is still unexplained and is not to be regarded as characteristic of old age. Lesions, changes, occur but not what is ordinarily recognized as inflammation. There is no myocarditis, as this phrase is generally understood. I shall return to this subject.

Of anatomic changes, I have traced two varieties, first that connected with what is already known of aging in heart muscle, its desiccation, its pigmentation, its changed nucleus; second that connected with what is already known of new elements as evidence of inflammatory processes and of connective-tissue growth. It is just as, perhaps even more, important to study the heart of advanced age from the viewpoint of *function*. Two orders of disability require examination—weakness and pain. *Weakness* must, it seems, be distinguished from fatigue. By fatigue, I mean a phenomenon which is asymmetric to, out of tune with, the performance of other still vigorous structures and organs. Except for this manifestation on the part of the heart, they continue to be capable of exhibiting the behavior of robust health. By weakness, I mean that phenomenon of symmetrical disability which, as the result of age, involves the whole organism in uniform progressing decrepitude. Similar phenomena may perhaps characterize cachectic states as in malignant neoplasms or pernicious anemia. But these I think fall outside my definition in that in some way their development may be found to be asymmetrical, inharmonious. Weakness, on its anatomic side, I have just been predicating, so far as contemporary knowledge permits, as the desiccation and pigmentation and perhaps other changes still unknown of the heart muscle. It may perhaps be regarded as the most natural of the manifestations of involution. The pump, without putting too fine a point upon it, is, after all, the life-distributing organ of the body. Its estate is still high, even if the estimates of a later physiology have displaced it from being, in Harvey's phrase, the sun of the microcosm. For the body to become weak, for the heart and indeed all the tissues to become desiccated and to undergo the many other chemical and physical changes which are easily conceived to be necessary if the

equilibrium of the forces and substances which are involved is to be maintained in harmony, is the natural result in the aging organism. How long the span of this process may be, whether if it be a lingering sweetness, it may be long drawn out, experience does not yet tell us. But of one thing surely there may be certainty; this process cannot be prevented by any means so far discovered. Hope, if hope it be, which is held out in this direction seems bound in some sense to be frustrated. Of far greater usefulness is the effort by whatever hygienic or other means to provide an environment in which the aging process may be accomplished to its best and most undisturbed advantage.

I come then to that most vexed problem of *pain*. There is little doubt, as Stewart[24] has pointed out, that the circumstances under which it occurs are now differently described from those which Heberden first indicated. Nor are there now many observers who believe that affection of the heart can give rise to one variety of pain only—either in distribution or in character. There is pain which is slight and brief and recurs during a long term of years; there is pain which, though brief, is intense and is accompanied at once by death. There is pain which is scarcely experienced at the precordium without radiating, but there is also pain which does not radiate. There is pain which does not raise the suspicion that it emanates from disorder of the heart; it is referred to the abdomen and is described as "severe stomach-ache" or "acute indigestion." There is pain which occurs only in connection with exertion, as in Heberden's description, designated as angina pectoris; but there is also pain which occurs in sleep and in the dead of night.

It is unnecessary to recall how difficult, how impossible it is to distinguish these varieties with the hope of assigning all of them to appropriate lesions. They differ in location, in duration, in radiation, in character and in the time and circumstances of their occurrence. Despite all the thought and investigation which has been devoted to this matter, only two structural abnormalities have been proposed for correlation with pain. Both are lesions of the coronary vessels. Herrick[25] deserves credit for having discovered what appears to be a sound anatomic basis for one variety. I refer to the association, not the lesion. The condition now is designated *thrombosis of the coronary artery*. It is not my purpose to describe this disease, if disease it be, in detail. There seems little doubt now, because of the nature of the pain, the presence of fever, leukocytosis, and pericardial friction rub and the coëxistence of thrombosis of a coronary artery, that this complex at least is a clinical entity. I wish rather to examine into the classification of this entity—into the age, and the nature of the lesion and then to indicate whether an understanding of prophylaxis and therapy are better served by regarding its occurrence as a manifestation of the aging process or straightway simply as a disease. Since its histogenesis is unclear,

an enquiry concerning it may repay study. On two points, there is knowledge. First, there occurs involution of the capillary vessels throughout the body and presumably also in the heart. Whether this process is a matter only of number or whether in addition a qualitative change develops in the endothelium is unknown—but a subject this of first importance. Second, there is an involution, as Gross[21] has shown, in the number of vessels of the heart. A third point may be added; Winternitz and his pupils to whose investigations I have already referred have insisted that in many arterial lesions the essential alteration is to be found in the vasa vasorum and that it is the alteration in them which is essentially connected with the occurrence of thrombosis. I am not aware that specific study has been made of this process in the coronary artery. The final link in the chain of argument is there. If thrombosis of the coronary artery depended on capillary involution, and if it were this essential process which underlay the occurrence of thrombosis of these particular vessels, there would be a somewhat clearer understanding of the whole matter. Meanwhile, one can do no more than say "somewhat clearer" because there remain other factors which still require analysis. Is this the method which accounts for the reduction in the number of vessels throughout the heart in advanced years? The situation is obviously different from that in early growth in which the number of vessels respectively in the walls of the two ventricles undergoes a state of relative change. It is not known to be a fact but the difference between youth and age may depend in this respect on the maintenance of a fixed number of vessels in which mere enlargement, expansion, occurs as the bulk of the right ventricle increases, but on the development of new vessels on the left side. The problem of increase and decrease in numbers need in short not be the same in youth and in old age. But to return to the situation in old age. If this is the process in the cases which are now familiar, is it this same process of capillary involution as just suggested, which is responsible for the natural disappearance of other vessels, and, if so, does evidence exist histologically that these others have gone this same course: and again, if so, how does it happen that change in these others is not accompanied by clinical manifestations? These are questions which are more readily asked than answered. The suggestion may, however, be ventured that, as a statistical matter simply, the chances are that smaller vessels, being more numerous rather than larger ones, are involved; that in consequence smaller areas, or volumes, of muscle are affected; and that, therefore, being relatively speaking silent no injury results sufficiently great to occasion clinical manifestations. But it is not even necessary to suppose that even small occlusions occur without the occurrence of distress; many an individual in middle life experiences some sort of discomfort on occasion—it may be trifling and passing or even transient severe pain; it may be the sensation of

premature contractions; it may be that because he has complained electrocardiograms are taken and reveal small or sometimes striking changes in their essential form. Who knows but that these are the cases which, in the absence of all other reasons, exhibit postmortem the appearance of disseminated sclerosis or of old infarction. Wearn[26] believes he has found it; others are silent or doubt whether it occurs. The collection of leukocyte counts and of temperature curves taken at such times may in the light of subsequent events yield important evidence, if this is the natural course.

The process which I have described may be, I am suggesting, at the root of thrombosis of the coronary arteries. I mean to be careful merely to suggest its possibility because of the use I wish to make of the suggestion in the subsequent argument, and to do no more than to propose it for further exact investigation. A knowledge of the fate of the capillary vessels at the end of life, as at the beginning, is a matter of first importance. If the assumption may tentatively be made that thrombosis of a coronary artery depends on the involution of capillaries, of vasa vasorum, the inference is justified and clear that the affection is incident to the process of growth, of continuing differentiation. Its occurrence is no accident, as an infectious disease is an accident, but a major among many similar minor occurrences, attaining conspicuous proportions merely as a matter of chance by involving a large rather than the usual small vessel.

I am aware of the fact that this view has important consequences for a general definition of disease. May it not disturb the usually accepted notion of the nature of certain diseases, so-called, of the kidneys? How shall affections like diabetes insipidus or indeed certain, especially youthful cases, of diabetes mellitus be classified? How affections attributable to other malfunctions of the glands of internal secretion? How that melting pot now designated arteriosclerosis? I do not raise the issue with the view to proposing solutions now for all these questions. They must be studied each on its own merits. It may very well be that in connection with growth, with the differentiation of the body, its tissues and organs, two possibilities exist. (1) An affection may develop in the embryo because growth has taken abnormal courses due to coarse processes of maldevelopment as in cor triloculare, or spina bifida or perhaps idiocy. (2) The malignant tumors, exophthalmic goiter, and pernicious anemia may belong to a group where the defect is more subtle. In old age, on the other hand, there need have been no initial defect in growth—growth and differentiation may have taken place without error; all tissues may duly have come into being and have performed their usual functions. When, as in coronary thrombosis which I am proposing tentatively as an example, an accident of growth takes place, it is not an accident of development, but a chance incident in that further differentiation which we call senescence. Those who wish to call this accident a defect will wish to distinguish

between defects of evolution, the events of youth, and defects of involution, the events of old age. The great importance of both, from the point of view of therapeutics, is that at the moment there appears to be no prophylactic relief. For both, there may eventually be the possibility of rational interference, especially if or when the process which underlies the defect is understood; but that the therapeutic procedure be rational, irrespective of whether the defect has occurred by accident or design, is in each case the condition of effective interference.

I have dwelt at length on the subject of coronary thrombosis because of its class it is the best defined of the maladies of the heart and could for that reason serve as a more satisfactory illustration. The choice I have made may be unwise or incorrect but the thesis I am defending is, I believe, necessarily sound nevertheless. The body does grow; it does differentiate, it does age, and it dies. If it attains the total duration of its natural span, it dies by a mechanism as natural as the one by which in common parlance it grew.

*Angina pectoris*, though in many minds it no longer accords with the description which Heberden gave of it, is the second condition in which there is general belief that pain is associated with or is dependent upon abnormality or malfunction of some sort of the coronary arteries. The pain is different from that usually described in coronary thrombosis. There it is tearing—here squeezing and viselike; there precordial, here apparently more often referred to the abdomen; there it radiates, in its most characteristic form, to the left arm, here it fails to do so. What the state of the coronary arteries is, whether atheroma or sclerosis is present or simply spasm of a vessel, not yet sclerosed or sclerosed only in part, is a subject recently discussed with much penetration by Keefer and Resnik.[27] In their view, anoxemia of the muscle due to affection or disease of the coronary arteries or of the aorta brings on characteristic pain. Others certainly may still find objection to this conclusion. Whether Sutton and King's[28] and Pearcy's[29] experiments in dogs in which they managed at will, by constricting a coronary artery, each time to elicit manifestations of pain are valid representatives of the clinical condition, it is still too soon to say. Keefer and Resnik's analysis and these experiments are useful contributions toward a knowledge of the subject. Whether this affection is to be reckoned as a disease or as a manifestation of growth depends obviously on ascertaining its mechanism more precisely. The whole subject is still too vague. Obviously this too occurs, as coronary thrombosis does, in the old rather than in the young. The mechanism which Mackenzie proposed, exhaustion of the heart muscle or of acute dilatation in the sense that this occurs in other hollow muscular viscera, the vermiform appendix or the gall bladder, finds no favor with Keefer and Resnik any more than does that of Allbutt who regarded this phenomenon as initiated at the root of the aorta.

But the condition itself is too ill defined, its pathogenesis and mechanism still too inexactly understood to render an attempt at classification profitable.

Although usually not described in textbooks, there is a form of *pain* which occurs in the *middle aged*, of great interest and, so far as is known now, not associated with a demonstrable cardiac lesion. It occurs, as did that in Heberden's description of angina pectoris, in association with exertion and with exertion only. Prolonged rest of two, three, four or even more months relieves such cases; and certain ones, though which they are it is difficult to predict, it relieves permanently. Whether this variety is associated with an anatomic lesion in the usual sense is not yet known.

On the assumption that heart muscle as well as all the other tissues in the body, no doubt are in a state of constant differentiation, questions arise concerning the possibility of *repair* after an injury is inflicted or of compensation after a mechanical defect has developed. Unfortunately, knowledge in both respects is meager. Warthin,[30] Heller[31] and others have shown in the case of diphtheria that in place of muscle which has been destroyed, new muscle fibers may develop. How frequent this is, and whether it is the rule is a matter about which one would like to know more. It was not an unexpected discovery, for in the growth of heart muscle there are investigations which indicate that differentiation may take place at a suitable time from persisting still undifferentiated cells. But the problem cannot yet be regarded as finally solved. In any case, it concerns young, not aged individuals.

That compensation for defects takes place is amply demonstrated in the case of valvular heart disease. Its mechanism is hypertrophy, enlargement of the individual elements of the muscle fibers, so far as is now known. It has been shown by MacKay, Addis and MacKay,[32] by Arataki[33] and others that under certain experimental conditions the kidneys also exhibit this function of hypertrophy. But it has likewise been shown, that this is a function of time and that after a while it declines. Whether a time occurs when it fails entirely is unknown, though by inference this is unlikely. The rate may be much delayed, but skin healing does take place in the aged and fractured femurs do unite. The important point is that the difference between adolescent and senile reactions is striking. Those pathologic anatomists whom I have consulted have the impression that, although precise knowledge still is sadly wanting, compensation in the form of hypertrophy is a form of repair in old age which, if not wholly lacking, is nevertheless significantly incomplete.

**Therapeutics.** Concerning therapeutics, I wish to speak of two matters only, the use of digitalis and the meaning of operation performed on the cardiac nerves. There are those who think that giving *digitalis* to older individuals is accompanied by less strikingly beneficial results than when given to the young. The justification

for this statement is still largely unfounded. There are undoubtedly among patients individual differences; they are plentifully familiar in the young. But in addition it is necessary to make a number of distinctions of importance. In the first place, cases of pure affection of the heart must be separated from those in which the kidneys are also involved and in which there is edema. In the second place, the type of cardiac affection which is present should be described. In the third place, it matters what the rhythm is to which the heart is subject—whether the auricles fibrillate or flutter. These and other considerations require analysis. At the present time, though, as has been stated, insufficiently founded, the belief prevails that digitalis is a less effective remedy in the senile state. What the principles of a sound digitalis therapy are must await further investigation. Meanwhile, there can be no reason for withholding the drug from patients in which on general grounds it appears to be indicated.

What the meaning of *operating on the cardiac nerves* is, is intimately related, obviously, with the whole subject which I have been discussing. This problem must naturally be decided quite apart from any question of operative technique or of the selection for treatment of the particular structures which will ultimately be found to be part of the nervous pathway involved in the occurrence of pain. The whole matter is one of great interest not only in therapeutics but from the point of view of anatomy and of physiology. Many patients have in fact been materially relieved of pain by one or another of the operative procedures.

Section or excision of a nerve may have or may interfere with one of several possible functions. It may cut the reflex arc which is instrumental in causing pain. If it does that and nothing more, no harm, but benefit only may be expected to result. But whether it interferes with, alters or stops the process which gives rise to the pain is not yet known. There are those who have hesitated to advise the use of the method lest patients be led to believe in a false security, when, in point of fact, the absence of a warning pain may induce them to undertake exertions and to become exposed to dangers which it would be better to avoid. Other things being equal, the question may be raised as to whether the exchange of comfort for danger may not depend on a decision in which the wishes of patients may perhaps be consulted.

But more may be involved in an operation than simply influencing pain. The time is not long past when Gaskell was maintaining theses concerning anabolic and catabolic functions of nerves—in this connection the anabolic function of the vagus nerves. The form in which he held his view seemed subsequently to require modification in the light of experiments and deductions therefrom performed by Einthoven. But phenomena, such as Charcot joints, to mention only one of them, point to the trophic functions of nerves. It is impossible to say now whether cardiac nerves have such functions

nor if they have, by which ones they are exercised. If as is possible certain of the affections of the heart depend upon the processes of growth, the influence of appropriate nerves may not be negligible. Interference may either accelerate or retard the process. To stop the pain may actually injure the patient. Experience, not taking thought, will solve the problem.

It was not my intention to present the subject of aging of the myocardium in a systematic way. What systems there are, may be found in the textbooks. But if I have understood the purpose of this program correctly, one which reflects an interest relatively speaking new, and matured in a period of time surprisingly brief, since first I devoted my attention and interest to it, it must be to lay before you points of view or at least a point of view which has not been, because an interest in the natural history of man (apart from that slight spread interest in constitution as a factor in etiology) has not been current in discussions on the content or range of medical science. It has been my object to emphasize the fact that human beings are growing creatures. Their anatomy and physiology cannot be described completely if the description is made to apply to a selected period of life. Growth is a continuous process, always in the throes of change, constantly exhibiting new and altering phenomena until the phrase, "the child is father of the man," takes on new meaning. Child and man are indeed two distinct individuals. If their natures are different, so are the ills to which they are liable, and so the remedies which it is the high function of medicine to bring to their relief.

**Summary.** A more formal summary of what I have attempted to bring to your notice, should, I think, not omit reference to the theories which have been evolved to make clear to men's minds how old age may be brought about; I refer to what were called mechanistic and teleologic theories. They form the background which make understandable the detailed researches which were later briefly described. Researches which aid in illustrating this manner of trying to understand changes in the growth processes were cited, both from the point of view of anatomy and of physiology in general, but especially certain ones which show that in connection with the circulation, studies already undertaken, not always consciously, make it certain that profit will flow from more deliberate investigations designed from this point of view. Certain diseases, if so regarded, appear to depend for their explanation, as I pointed out, on the processes of growth, rather than on accidents dependent on the external environment. If a division of diseases due to accidents, on the one hand, and on the other to defects in growth issues from reflection of this sort, the significance of certain cardiac maladies, of which pain is a prominent complaint and which occur in advanced years, takes on a new or a different meaning, not only in comprehending their pathogenesis but also in making provision for their relief.

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## INTERVENTRICULAR SEPTAL DEFECT WITH DEXTROPOSITION OF AORTA AND DILATATION OF THE PULMONARY ARTERY ("EISENMENGER COMPLEX") TERMINATING BY CEREBRAL ABSCESS.

### Report of a Case Observed during Life, Presenting Impaired Conduction, and Paralysis of Recurrent Laryngeal Nerve from Pressure of Hypertrophied Pulmonary Conus.*

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Cases of interventricular septal defect with associated pulmonary stenosis and dextroposition of the aorta (tetralogy of Fallot), are not infrequent in the literature; but the combination of a localized defect in this situation with dextroposition of the aorta but *without* associated pulmonary stenosis is extremely rare. The first case on record is a full clinical and pathologic study published by Eisenmenger,[1] in 1897, of a cyanotic man, aged thirty-two years, in whom the combination was correctly diagnosed during life by von Schrötter from the character of the physical signs, in that the loud precordial systolic murmur present was not transmitted into the vessels of the neck as is usually the case in the "tetralogy" but downward toward the apex and along the course of the pulmonary artery, and there was no thrill. So far as we know only two other cases have

* Presented at the meeting of the International Association of Medical Museums, Albany, N. Y., April 1, 1926.

been reported, both by Abbott, one the heart of a child, a specimen in the McGill Museum, and the other a man, from the service of Dr. Libman, aged thirty-five years, who died of a subacute bacterial endocarditis.[2] Moreover, a case, of congenital cyanosis such as the following in which the patient has attained adult life and has been studied clinically with Roentgen rays and electrocardiogram, followed later by necropsy, is still more worth recording. The patient was seen in this clinic on four different occasions over a period of fifteen months and though the particular nature of the lesion was not specified, a diagnosis of congenital disease of the heart was made. Of special interest also, from the clinical standpoint were the following observations: (1) evidences in the cardiogram of an abnormal disturbance of the propagated impulse (left bundle-branch block); (2) hoarseness for many years, and more recently aphonia, due to pressure on the recurrent laryngeal nerve of the enormously hypertrophied conus of the right ventricle, which showed in the Roentgen ray as (3) a greatly enlarged pulmonary arc (Fig. 1); (4) the termination by left hemiplegia with coma, shown by the subsequent autopsy to be due to a large cerebral abscess in the right frontoparietal lobe. The latter event is of great interest as pointing to a paradoxical embolism into the greater circulation of septic thrombotic masses from the venous circulation, an accident peculiarly liable to happen under the anatomic conditions present, in which a large dextroposed aorta rode above the defect receiving blood through it from both ventricles (Fig. 5). Following is the report of this most interesting case:

**Case Report.** V. B. (Case No. 17098) male, aged twenty years, entered the Clinic on account of a goiter and hoarseness and aphonia. He was seen early in March, 1924, giving a history of hoarseness and aphonia since about the age of thirteen years. The patient had never been strong but had lived on a farm and done many of the tasks there necessary. He had a small goiter which had been present some months and which was the main reason for entering. There was lack of endurance, dyspnea after increased exercise and cyanosis of dependent parts. In the family history there was one brother who had a goiter. The parents were rugged farmers who had always been well and did not understand the shirking in work that ill health may force on one.

The examinations were directed mainly to the heart and the possible effect of the goiter on the cardiovascular system. On fluoroscopic chest examination, a general hypertrophy with marked prominence of the right auricular curve and slight prominence of the left was noted. The pulmonary conus was unusually prominent, the heart action rapid, overactive. Pulsation was transmitted especially to the right hilum and pulmonary conus. No substernal thyroid was seen nor was the liver or spleen visualized. A slight increase of hilum shadows was noted.

In 6-feet heart films the measurements showed a moderate general hypertrophy. The curve of the right auricle was decidedly prominent, the right ventricle full and rounded, the left auricle prominent, but shaded over by a *marked prominence of the pulmonary conus* (Fig. 1). The roentgenologist's conclusion was that this was a congenital heart condition, most likely a pulmonary stenosis with patent ductus arteriosus (Botalli) and a general hypertrophy, especially of the right side.

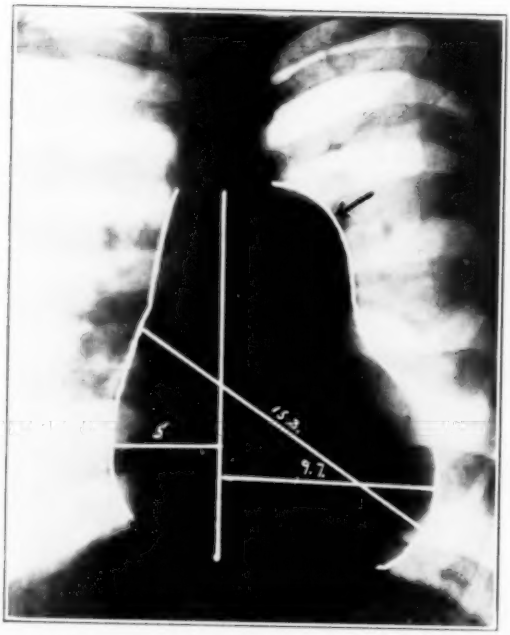


FIG. 1.—Teleoröntgenogram (6 feet) taken of the heart at the first entry.

| Heart Teleoröntgenogram | Weight Average normal 125 or 130 |
|---|---|
| M. R. 5 | 3.7 |
| M. L. 9.7 | 7.2 |
| T. D. 14.7 | 10.9 |
| L. D. 15.3 | 12.6 |

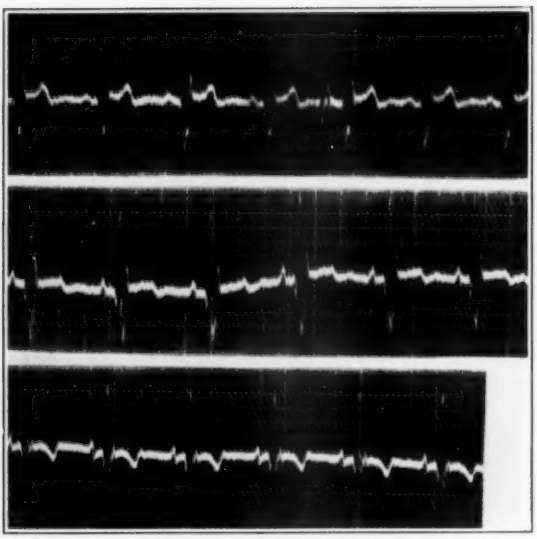

FIG. 2.—Electrocardiogram (Leads 1, 2, 3) taken at the first entry, showing right ventricular preponderance and split $R$ and $S$ waves. The $Q$–$S$ interval is 0.09 seconds.

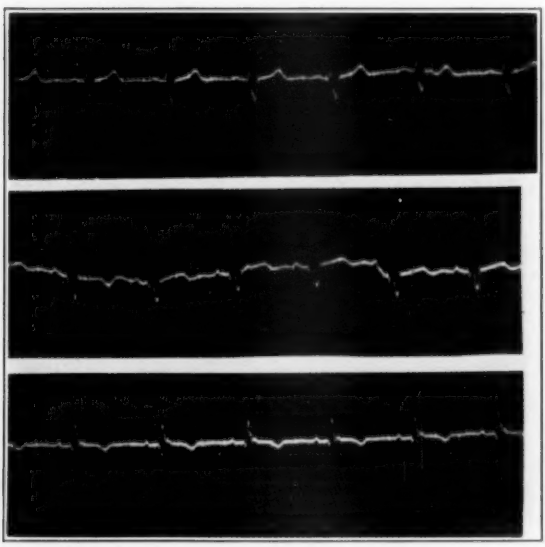

FIG. 3.—Electrocardiogram taken June 4, 1925 (third entry), showing right ventricular preponderance split $R$ and $S$ waves. The $Q$–$S$ interval is 0.10 seconds.

Auscultation showed a loud systolic murmur over the heart, most marked in the pulmonic area, and a soft diastolic one to the left of the sternum. A cardiogram showed right-heart preponderance and a split *R* and *S* (Fig. 2). It was thought there was a congenital pulmonary stenosis and hypertrophy of the heart.

Eight months later the patient was again seen. At this time, a note was made that the patient was less easily made cyanotic and the diastolic heart murmur was not so loud as in the previous examination. The blood pressure was 110 systolic, 80 diastolic. There was some cyanosis of the peripheral parts, dyspnea on exertion and a loud systolic murmur over the pulmonic area. Cardiogram again showed a split *S*, a right heart preponderance, and slight delay of conduction thought to be evidence of incomplete left bundle-branch block.

Seven months after his second entry the patient returned. Again slight exertion caused dyspnea. His color was definitely better than at the previous visits, but was said always to be better in warm weather. A loud systolic murmur over the precordium and a diastolic to the left of the sternum louder than at the previous examination was noted. Blood pressure was 100 systolic, 70 diastolic. Cardiogram showed a split *R* and *S*, a right-heart preponderance and again evidence of left bundle-branch block (Fig. 3). The patient had returned on account of the thyroid condition. It was not thought this was causing any toxic symptoms so far as the heart was concerned.

On his final entry, July 28, 1925, the patient was practically comatose. About two weeks previously headaches began but he continued light work. He became nauseated, vomited and finally several days before entry became drowsy but could easily be roused. On entry, there was found a bilateral choked disk, paralysis of the left face and arm and an ill-sustained ankle clonus on the left. A loud, harsh systolic murmur best heard over the pulmonic area was again noted. He was given salt solution intravenously. The next day there was no nausea or vomiting, the pupils were dilated, the left leg was partially paralyzed and the left arm was noted as weaker than on the preceding day. Lumbar puncture showed increased pressure of the fluid, a cell count of 9, positive globulin but a negative Wassermann. The blood Wassermann was also negative. One specimen of urine showed sugar but another was negative for this, albumin was slightly positive, and many leukocytes were present. Speech became difficult, the heart rate was between 40 and 50 and the patient complained of much headache, but toward night became comatose. The next day the pulse became more rapid and he died early on the third day.

*Autopsy* revealed a rather slightly built and poorly nourished young adult male. The heart *in situ* was horizontal, the right auricle and ventricle markedly enlarged and the pulmonary artery enlarged, especially so in comparison with the aorta (Fig. 4). The pulmonary artery at the base of the valve measured 8.5 cm. and the aorta 6 cm. The left ventricular wall measured about 12 to 13 mm. in thickness. The pulmonary cusps were fenestrated and of unequal length, the posterior one being very voluminous and 3.5 cm. long, the left anterior 3 cm. while the right anterior was comparatively short, only 2 cm. in length. There was a small accessory coronary given off behind the left anterior pulmonary cusp. The mitral valve, as well as the aortic, was normal. The right ventricle wall measured 10 to 11 mm. in thickness. In the upper part of the interventricular septum just anterior to the pars membranacea septi there was a defect 2 cm. across (Fig. 5). The anterior and lower borders of this were muscular and rounded. The fibrous tissue of the right posterior aortic valve was continuous with the pars membranacea, and the medial tricuspid segment which formed the wall of the septal defect. The aorta arose partially from both ventricles

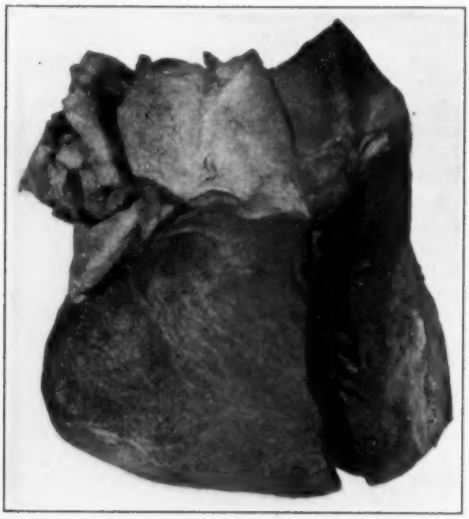

FIG. 4.—Photograph of heart showing right ventricle and pulmonary artery opened up. Note the thickness of the conus wall and the width of the base of the heart.

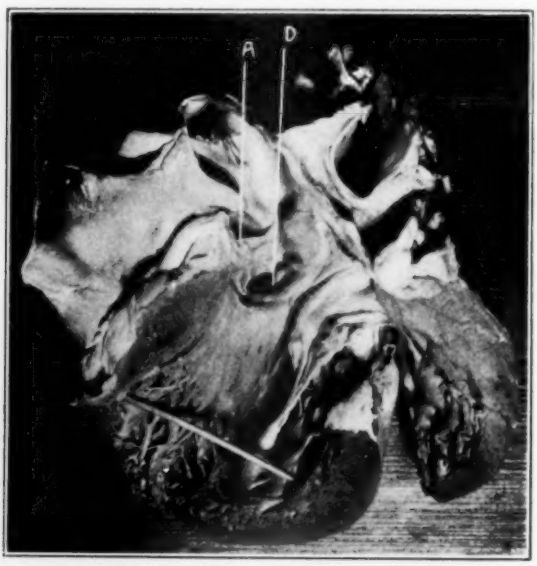


FIG. 5.—Photograph showing defect in ventricular wall through the opened left ventricle. *A*, right anterior (coronary) cusp. *D*, interventricular defect. Note thickness of ventricular wall.

and appeared rotated somewhat to the right (dextroposition). The conus of the right ventricle leading to the pulmonary artery was somewhat narrowed and had thick powerful muscles, the posterior muscle wall forming the anterior wall of the septal defect being especially thick. The tricuspid valve presented a deformity of the contiguous halves of its medial and infundibular segments which were attached without any proper differentiation of papillary muscles, the infundibular cusp into the posterior surface of the heavy muscular wall of the conus of the right ventricle which here forms the anterior boundary of the septal defect, while the left end of the septal tricuspid segment is in part fused with the contiguous margin of the infundibular segment but in greater part passes through the septal defect and after becoming continuous with the anterior segment of the mitral valve below and with the pars membranacea above, is attached here to the aortic ring just below the junction of the right posterior and anterior (right coronary) cusps. It thus serves to screen the large septal defect in the right half of its extent from the cavity of the right ventricle. A single, long, thick aberrant chorda tendinea passes from the free portion of the infundibular tricuspid segment to be attached by three branching filaments to the anterior border of the defect near the attachment of the main infundibular segment to this area. No signs of acute inflammation were found. A loose thrombus in the right auricle which was afterward observed is discussed later in this paper.

The thyroid showed a rather definitely enlarged left lobe, about three times the size of the right. On section, many small nodules were to be seen, some continuing dark-colored fluid. The right also contained small nodules. In the brain, the convolutions over the right frontoparietal area were flattened and an irregular yellow area was seen on the surface; this was soft to the touch and purulent material was obtained on puncture. Culture showed a Streptococcus hemolyticus. After hardening the brain, section showed a large abscess about 5 cm. across in the right frontoparietal region involving the motor area, internal capsule and surrounding structures. Microscopic studies showed a typical abscess of the brain and an adenoma of the thyroid.

**Discussion.** We have then here some typical findings of a congenital heart case with some confusing symptoms. The hoarseness was thought possibly due to the thyroid although this was not markedly enlarged. No disease of the larynx or trachea could be made out. Because of a possible goiter operation the heart was studied and a congenital lesion believed to have been found. From the enlarged right heart and high pulmonary arc and location of the murmurs, it was thought a pulmonary stenosis with persistent ductus arteriosus was the probable lesion. It was acknowledged at the bedside that the aphonia might possibly be accounted for by the enlarged heart, but at the time the thyroid was believed to be the cause. In his final entry, a diagnosis of increased intracranial pressure was made, but operative procedure was thought inadvisable on account of the heart condition.

Abbott, Lewis and Beattie[3] have published two cases of interventricular septal defect with associated pulmonary stenosis and cerebral abscess following embolism, and collected 6 similar cases from the literature. These varied from six to twenty-five years of age. There were 6 males and 2 females in the series. They have

also collected 6 cases of open foramen ovale with brain abscess. Their explanation of a paradoxical embolism is apparently well-grounded. Their 2 cases had definite sources of emboli, in one an infected arm, in the other an acute appendix. Our case is less clear in this point as there was no endocarditis or septic lesion located, and the only source for an embolism that was demonstrable was a small pocket in the wall of the right auricle near the entrance of the superior cava containing loose thrombus, which was not noted at the autopsy but was located later in the Museum specimen.

Abelmann[4] in discussing heart anomalies made the statement that these cases often die with brain symptoms. He did not, however apparently understand the significance of the brain symptoms as originating in a "crossed" embolism as did Ballet[5] (1880), and as has been so clearly pointed out by Abbott and others.

In comparing our specimen with those described by Abbott and her associates[3] in their article on this subject, we see that it corresponds to their 2 cases in the presence of a huge interventricular septal defect above which the aorta is displaced to the right, thus supplying a direct avenue for the transmission of an embolus from the right heart to the great vessels of the head and neck and brain. It differs however from their cases in the absence of pulmonary stenosis (as in their Case 2), or atresia (their Case 3), for the pulmonary conus in the case here described is roomy and thick-walled, and leads into a very large and greatly dilated pulmonary artery (8.5 cm. wide). Both conus and artery have here developed as in the normal heart, and have evidently undergone dilatation to accommodate the additional volume of blood received from the left ventricle through the defect in the left to right shunt that prevailed owing to the relatively higher pressure in the left ventricle, while the dextroposed aorta received a mixed current of venous and arterial blood from both ventricles above which it rides and transmits this to the systemic circulation, producing a raised oxygen-unsaturation in the capillaries there with resultant cyanosis (see Fig. 6 from Abbott and Dawson[6]). Clinically our case resembled pulmonary stenosis with associated septal defect in that there was a harsh precordial systolic murmur which on three occasions was observed to have its maximum intensity at the pulmonary area, and there was no thrill. On one admission, however (June 1925), it was described as diffusely heard over the entire precordium (that is, without point of maximum intensity) and there was always present along with it a distinct diastolic murmur on the left side of the sternum which was apparently the result of the pulmonary insufficiency, while the Roentgen ray plates, which show only a moderate (though definite) right-sided enlargement, with marked enlargement of the pulmonary arc, and the fluoroscopic demonstration of marked conus pulsation in this same arc with widening and increased pulsation at the hilum of both lungs (Assmann's sign) pointed definitely to a pulmonary dilatation (and

not to a stenosis as has been wrongly argued by some writers). Again, the late onset of the cyanosis at about the age of thirteen years, and the moderate degree of this that existed, together with the absence of clubbing argue also against the existence of an associated pulmonary stenosis, in which condition the combination of back pressure in the venous circulation resulting from the pulmonary obstruction combines with the high venous content of the arterial blood under the right to left shunt that prevails, to produce marked cyanosis and clubbing in all cases of long standing.

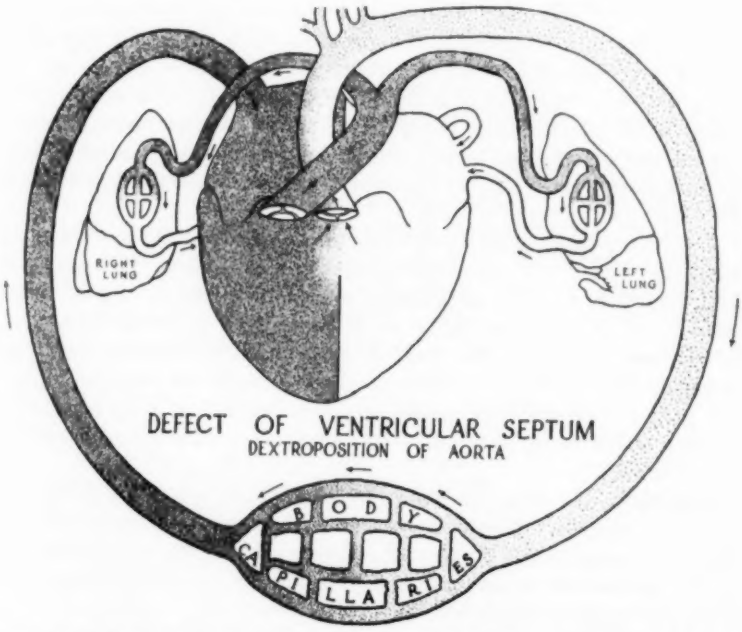


FIG. 6.—Diagram showing course of the circulation in interventricular septal defect with dextroposition of the aorta and dilatation of pulmonary artery (Eisenmenger type). The aorta is seen to ride over the defect, receiving arterial and venous blood from both ventricles leading to a moderate degree of cyanosis. (From Clinical Classification of Congenital Cardiac Disease, by Abbott, Maude E., and Dawson, Wilfred T., *International Clinics*, 1924, **4**, 170, Fig. 9.)

In this case, therefore (in which it must be clearly emphasized there was no pulmonic stenosis), the presence of the enlarged pulmonary tract was clearly evidenced by the above syndrome, while the dextroposed aorta and ventricular septal defect were indicated by the moderate degree of cyanosis, and the curious shape of the heart in the Roentgen ray picture, which shows a widening to the right of the median line above, and a relatively small degree of enlargement of the right heart, the hypertrophy of the latter being apparently mostly confined to its conus portion. The cardiogram

is also of some diagnostic value in that the partial bundle-branch block in the later examinations suggesting possible injury to the conducting system, points to the presence of the ventricular septal defect. That is to say, although in a number of recorded cases of ventricular septal defects these fibers have undoubtedly escaped and no interference with conduction has occurred, there are a sufficient number of others in which they have been definitely proved to have undergone deflection and interruption with resultant partial or complete congenital heart block. Of this the most classic illustration is the recent carefully investigated specimen reported by Wilson and Grant.[7] The electrocardiogram may be taken therefore to be further evidence suggesting the presence of a defect of the interventricular septum, while the right predominance points to the presence of a complicating lesion leading to hypertrophy of the right heart which, since pulmonary stenosis could have been excluded (see above) one might well have concluded in the light of the symptomatology to be the dextroposition of the aorta that actually did exist.

An interesting phase was the terminal streptococcic cerebral abscess. There was no endocarditis, and no history nor source of infection from which a paradoxical embolism might be traced, but it is believed by us that some such focus was present. The collected cases[3] make it clear that in the presence of brain symptoms in congenital heart cases, cerebral abscess should be considered, and the presence of cerebral symptoms in conjunction with signs of a cardiac abnormality may actually clinch the diagnosis of a cardiac septal defect.

**Summary.** 1. The combination known as the "Tetralogy of Fallot," namely, pulmonary stenosis, ventricular septal defect, dextroposition of the aorta and hypertrophy of the right ventricle, is the commonest of all cardiac abnormalities in cases of congenital cyanosis reaching adult life.

2. A case in a male adult observed during life with the help of Roentgen rays and electrocardiogram and confirmed by necropsy, is here presented. There was found a large interventricular septal defect with dextroposition of the aorta but without any pulmonary stenosis or hypoplasia. This differs, therefore, from the classic "tetralogy" in that the pulmonary conus, orifice and artery are normally developed and have undergone dilatation as a result of influx of blood from the left ventricle through the defect into the pulmonary circulation.

3. Such cases as this of pulmonary dilatation with ventricular septal defect and dextroposition of the aorta have been described by Abbott[8] as of the Eisenmenger type, after the author who published the first case on record, and are relatively rare. Clinically, this condition is differentiated from the "tetralogy" by the more moderate degree of cyanosis and clubbing (as is evident from the

anatomic conditions which are more favorable for oxygenation), the localization over the precordium of a harsh systolic murmur generated at the defect and not transmitted into the vessels, the occasional presence (as in the present case) of a diastolic murmur of pulmonary insufficiency, and the distinctive character of the Roentgen ray picture which shows in cases with well-marked pulmonary dilatation as in the present one, a large pulmonary arc and increased hilum shadows, as well as a broadening of the aortic shadow to the right above the base (dextroposition), and a more moderate degree of right-sided enlargement than would occur in the "tetralogy." These features of the Roentgen ray are shown in the present case (Fig. 1) in exquisite pronouncement.

4. In the presence of the above complex the evidence supplied by the cardiogram, of interference with the conduction bundle is also of diagnostic value, as suggestive of an interventricular septal defect, such as actually existed here.

Termination by cerebral abscess is especially liable to occur in a ventricular septal defect with dextroposition, for this combination supplies a direct path for the transmission of a "crossed" embolus from a septic focus in the lesser circulation. Although this focus was not located in the present case, it nevertheless adds another to the series collected and recorded[3,5,9,10] in which a lethal cerebral complication was associated with, and consequent upon, a cardiac septal defect.

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# FULMINATING MENINGOCOCCUS SEPTICEMIA WITHOUT MENINGITIS.

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and

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There are two possible modes by which the meningococcus may reach the central nervous system from its original place of lodgment in the nasopharynx. The lymphatic route was formerly considered the more frequent, especially in view of the large number of negative blood cultures obtained by workers with cerebrospinal meningitis. More recently, however, and especially since the World War gave opportunities for extensive observation,[1] it has come to be recognized that a meningococcemia very frequently occurs before localization of the infection. Herrick[2] has laid much emphasis on this point, and finds in it the indication for early and vigorous intravenous therapy. By this means, he reports a considerable reduction in mortality, particularly under military conditions where patients come under observation before the clinical picture has fully evolved. Herrick found positive blood cultures in 45 per cent of his cases.

In every epidemic, meningococcus infections are observed which run their course without metastasis to the central nervous system, being septicemic in nature throughout. For this reason Herrick[3] considers the expression "epidemic cerebrospinal meningitis" a misnomer, since it describes only one manifestation of a protean disease. He recommends that it be superseded by the terms "meningococcus infection" and "meningococcus meningitis."

Two forms of purely septic meningococcus infection occur:

1. A prolonged febrile state, characterized frequently by arthritic symptoms and a mild roseolar or petechial eruption. Prostration is often not severe. This form may resemble typhoid fever or malaria. Zinsser[4] says of these patients: "We advise a serious consideration of the diagnosis of meningococcus septicemia whenever a prolonged case of fever with leukocytosis and a slight variable rash comes under observation."

2. Fulminating cases with widespread purpuric blotches. In these death may occur very rapidly. In fact, it has been reported as early as four hours after the onset of symptoms.

The following case of the latter type seems worth reporting, since it illustrates the extreme intensity which meningococcus septicemia may develop without localization in the central nervous system, which we are so prone to regard as the important feature of these infections:

**Case Report.** K. M., a Norwegian seaman, aged eighteen years, was admitted to the medical service of Dr. George W. Norris at Pennsylvania

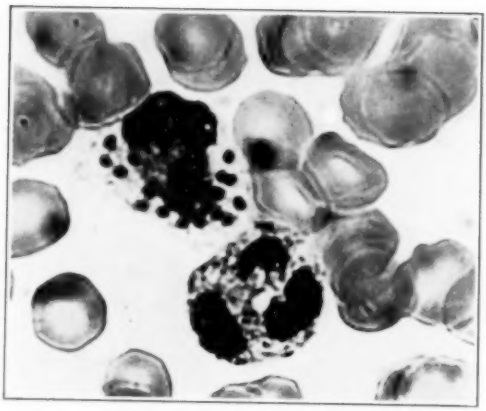

FIG. 1.

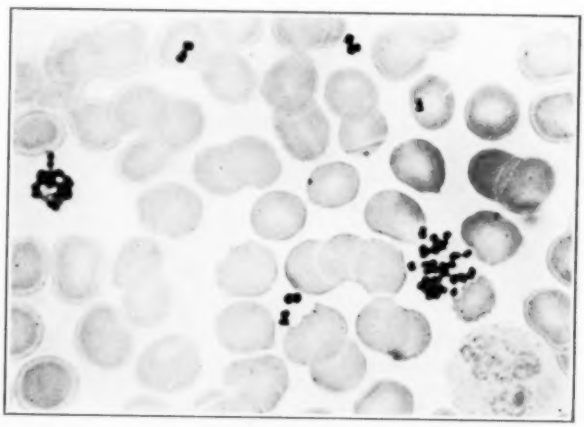

FIG. 2.

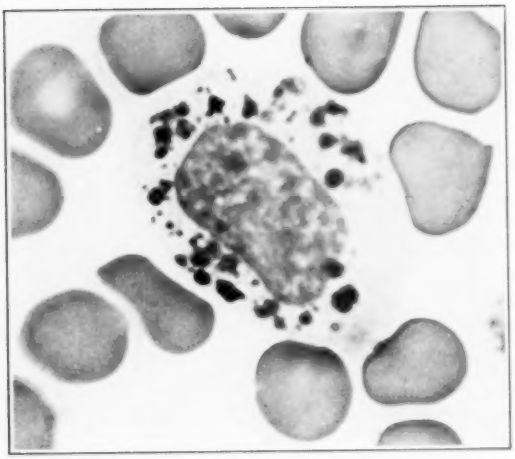

FIG. 3.

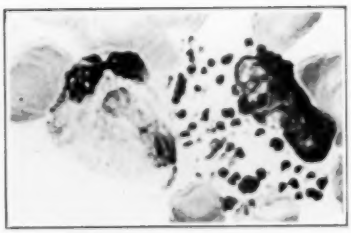

FIG. 4.

Hospital, March 23, 1928, at 10.30 P.M. He had been perfectly well until the morning of admission, when, about 9 A.M., he complained of headache. He had no chill, but felt feverish. He remained in bed all day and seemed somewhat stuporous. He vomited once in the late afternoon. In the evening, his uncle brought him to the hospital in a taxicab. On the way to the hospital, purple blotches were seen coming out over the patient's body. His skin had previously been clear.

The patient's past history was negative except for malaria, for which he had been treated four months previously in a hospital in Virginia. He was a seaman who had traveled widely in the Orient and Europe in the past two years. He had recently been employed on freight vessels going to the West Indies. He had been leading a quiet life visiting relatives in Philadelphia during the week preceding his illness.

On admission, the patient was delirious and very restless, tossing about in a semicoma from which he could be aroused to answer short questions. His skin was hot and dry, and covered everywhere with small and large irregular red blotches which did not disappear on pressure. These purpuric spots ranged from about 0.5 cm. to about 2 cm. in diameter. The pupils were small and did not react to light. There were many petechiæ in the conjunctivæ. The pharynx could not be well examined because of difficulty in managing the patient. There was slight stiffness of the neck. Examination of the lungs was negative. The heart rate was very rapid (160), but the sounds were of fair quality and no murmurs were heard. Blood pressure was 62 systolic and 50 diastolic. The abdomen was scaphoid, with no demonstrable tenderness or rigidity. Knee jerks could not be elicited. Kernig's sign was slightly positive; Babinski's negative.

Lumbar puncture was performed shortly after admission, a small amount of chloroform being required on account of the patient's struggling. Fifteen cubic centimeters of crystal-clear fluid were obtained. The pressure was 15 mm. of mercury, but the increase could be accounted for by the patient's movements. There were 12 cells per c.mm., but globulin was not increased (Pandy's Reagent). The colloidal-gold curve was later reported to be 0000000000.

A blood count made shortly after admission showed 4,170,000 red blood cells per c.mm. and 88,550 leukocytes, of which 64 per cent were polymorphonuclears, 22 per cent myelocytes, 10 per cent lymphocytes, 2 per cent large mononuclears and 2 per cent eosinophils. An ordinary cover-slip smear of the blood, stained with Wright's stain, revealed a large number of intracellular and extracellular diplococci, as shown in the accompanying photomicrographs. Single leukocytes containing as many as 30 pairs of cocci were observed. A similar blood smear stained by Gram's method—in which the red blood cells were dissolved, leaving large numbers of leukocytes loaded with diplococci—gave a picture closely resembling the smear from a fresh gonococcic urethritis. The organisms exhibited the marked variation in size which is so characteristic of the meningococcus.

The patient rapidly became completely comatose, with rapid, labored respirations and increasing cyanosis. The heart rate grew very rapid and the pulse almost imperceptible at the wrist. The suggestion of cervical rigidity did not develop into actual stiffness. The patient died at 12.40 A.M., March 24, 1928, about fifteen and a half hours after the onset of his illness.

A blood culture taken immediately after death yielded a vigorous growth of meningococci. These failed to agglutinate in type sera obtained from the Division of Laboratories and Research of the New York State Department of Health, but a good agglutination was obtained with polyvalent serum (Mulford). The organism thus belonged to a subsidiary strain. A blood chemistry taken within a few minutes of death gave the following values: Sugar, 30; urea nitrogen, 35; creatinine, 4.3 mg. per 100 cc.

**Necropsy.** The important necropsy findings were as follows: The body was that of a well-nourished and extraordinarily well-developed young white male. The skin was everywhere profusely covered with large, irregular purpuric blotches. Numerous petechiæ were seen on the conjunctivæ and on all visible mucous membranes. There was no free fluid in the abdominal or pleural cavities. All serous and mucosal surfaces of the abdominal and thoracic viscera were thickly studded with innumerable petechiæ. On section, the lungs were reddish-brown in color and bled freely, but no definite consolidation was noted. The mesenteric glands were all enlarged and Peyer's patches were markedly hyperplastic, but not ulcerated. The adrenals were enlarged, softened and hemorrhagic, being almost black throughout. Microscopic study revealed practically total destruction of adrenal tissue from massive hemorrhages.

On removing the calvarium, great engorgement of vessels and definite edema were noted over the cerebral convolutions. There was no evidence, however, of a purulent exudate over the hemispheres or at the base of the brain. A swab from the surface of the brain gave a sparse growth of meningococci in pure culture (autopsy not performed until thirty-five hours after death!).

The spinal cord was not examined.

**Discussion.** The remarkable feature of this case is the extreme intensity of the meningococcus septicemia. Although this is not the first time meningococci have been demonstrated in an ordinary blood smear, we are not aware that so many have been observed before. The mild cervical rigidity and slightly positive Kernig's sign suggested meningitis. The spinal-fluid findings, however, and later the necropsy, indicated that these signs were due merely to meningismus, which might occur in any similarly severe toxic process.

The strikingly low blood-sugar value and marked hypotension seem well accounted for by the bilateral hemorrhagic destruction of the adrenals discovered at necropsy. The total absence of adrenal secretion, with resulting failure of carbohydrate mobilization and vasomotor control may well have been the immediate cause of death.

It is unlikely that serum therapy could change the outcome of fulminating infections such as the one described. Such cases, nevertheless, serve to emphasize the importance of bacteremia as a feature of meningococcus infections, and indicate the desirability of vigorous intravenous therapy even when localization of the infection in the meninges seems to have occurred.

**Conclusions.** Meningococcus meningitis is frequently, and we believe usually, preceded by meningococcus bacteremia. Fulminating infections with this organism may occur and cause death within a few hours after the onset of symptoms, the only clinical and anatomic findings being those of an intense septicemia. Such a case is here described.

Vigorous intravenous therapy should never be omitted in treating meningococcus infections.

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# LEUKOSARCOMA.

## With Report of a Case Beginning with a Primary Retroperitoneal Lymphosarcoma and Terminating with Leukemia.*

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All degrees of lymphoid hyperplasia are illustrated in various types of disease of lymphoid tissue. At one end of the scale are the benign hyperplasias, and at the other end, the atypical and invasive lymphosarcomas. Between these are the cases of typical lymphatic leukemia, which show a generalized hyperplasia of the lymphoid tissue and a lymphemia. They usually have only slightly atypical cells and lack the highly invasive character of lymphosarcoma. Intermediate between this group and the lymphosarcomas are the cases to which Sternberg has applied the term leukosarcoma.[1,2,3] These cases are characterized essentially by the combination of a more or less localized, primary, and invasive lymphoid tumor and a leukemic blood picture.

A survey of the literature that we have made reveals at least 107 cases which appear to come in this group. The probable primary site of the invasive tumor is as follows: Mediastinum, 60; skin, 11; eye and eyelids, 11; retroperitoneal and abdominal lymph nodes, 6; pleura and peritoneum, 2; femur, 2; breast, 2; dura, 2; intestines, 2; axillary lymph nodes, 1; skull, 1; cervical lymph nodes, 1; lymph nodes generally, 1; ribs, 1; cervix of uterus, 1; ovaries, 1; tonsils, 1; prostate, 1.

In at least 16 cases, various observers have noted early in the disease the presence of lymphoid enlargements without blood involvement, and subsequently a leukemic blood picture ([4-16]). Of interest in this connection are 9 cases in which there was a similar story, but no invasive tumors ([17-25]). These cases suggest that in many other cases of leukemia there was an earlier local process which later was also manifest in the blood, producing leukemia. The case that we are reporting points toward this course of the disease.

* Presented before the Philadelphia Pathological Society, October 11, 1928.

**Case Report.** The patient, Edward B., white, aged sixty years, in July, 1926, noticed a swelling in the right inguinal region. This gradually increased in size and in March, 1927, lymphedema of the right leg and genitalia developed. He was admitted to the surgical division of the University Hospital on July 2, 1927, when a lymph node was removed from the inguinal region. The pathologic diagnosis by Dr. A. E. Bothe was lymphosarcoma. Roentgen ray examination on July 1, 1927, was negative for mediastinal glands, but showed in the pelvis a large mass which did not appear to be springing from the bone. Physical examination showed a general lymphadenopathy due to a moderate number of discrete, soft, nontender lymph nodes, from 0.5 to 2 cm. in diameter, and a large firm mass in the pelvis. The leukocyte count at this time was 7300 cells per c.mm. The patient was referred to Dr. Henry Pancoast for Roentgen ray therapy and was treated three times a week from July 12, 1927, to November 17, 1927. While he was under this treatment, numerous leukocyte counts were made, ranging between 5000 and 7000 per c.mm. The differential count showed 50 to 60 per cent neutrophils, 30 to 40 per cent lymphocytes, 3 to 10 per cent large mononuclear cells, and 2 to 3 per cent eosinophils. The percentage of neutrophils gradually diminished, and that of lymphocytes gradually increased. The erythrocytes ranged between 3,500,000 and 4,000,000 per c.mm. and the hemoglobin between 72 and 85 per cent. In September the mass in the abdomen was noted to be much smaller and the patient felt better.

About November 1, 1927, the patient developed a gradually increasing jaundice, and began to complain of weakness, anorexia, nausea, and palpitation. On November 10, 1927, the leukocyte count was noted to be 96,000 and on November 17, 1927, it was 100,000 per c.mm. The differential count showed 90 per cent small lymphocytes.

On November 21, 1927, he was admitted to the medical division of the University Hospital on the service of Dr. Alfred Stengel. The outstanding findings on physical examination were a vaguely defined, deep-seated mass in the right side of the abdomen, moderate jaundice, generalized adenopathy, signs of fluid in the right chest and marked enlargement of the liver. The spleen was not palpable. The blood count in November 22, 1927, was as follows: Red blood cells, 2,960,000; hemoglobin, 59 per cent; white blood cells, 96,000, and a differential count of small lymphocytes, 97 per cent; neutrophils, 2 per cent, and large mononuclear cells, 1 per cent. The Wassermann reaction was negative.

At this time the clinical diagnosis of leukosarcoma was made although the site of the primary invasive tumor was not definitely known. It was assumed, however, because of the Roentgen ray examination on July 1, 1927, which showed a large mass in the pelvis, that it had its origin in the retroperitoneal lymph nodes.

On December 1, 1927, the leukocyte count had risen to 288,000 with 96 per cent small lymphocytes, and on December 3, 1927, a few hours before death, the leukocyte count was 444,000. The average temperature was 100, the average pulse 100, and the average respiration 23.

*Surgical Specimen.* (Inguinal lymph node removed July 2, 1927.) The gross specimen was noted as being part of a lymph node 2.5 by 2.5 by 2 cm. On section it was light pink in color, with pin-point hemorrhagic areas. The capsule was noted as being in places 2 mm. in thickness.

*Microscopic Examination.* Throughout the node, there is an irregular alternation of lighter staining areas with darker areas (Fig. 1). The darker zones contain chiefly small lymphoid cells, while the lighter zones contain many larger cells which stain less intensely, show numerous mitotic figures, and are less compactly arranged. In places the lighter portions are round, resembling germinal centers. The sinuses and original architecture have

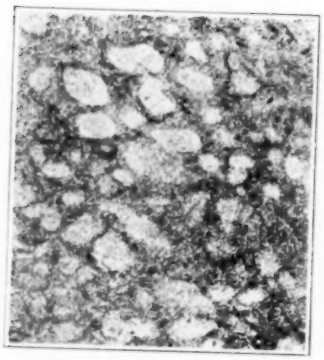

FIG. 1.—Section through a lymph node showing the tendency to form the lighter and darker areas of the tumor. Mag. 10×.

FIG. 2.—A group of lymph nodes from the right axilla. The loosely attached, uninvaded fat was dissected away, leaving very discrete nodes. Compare with Fig. 3.

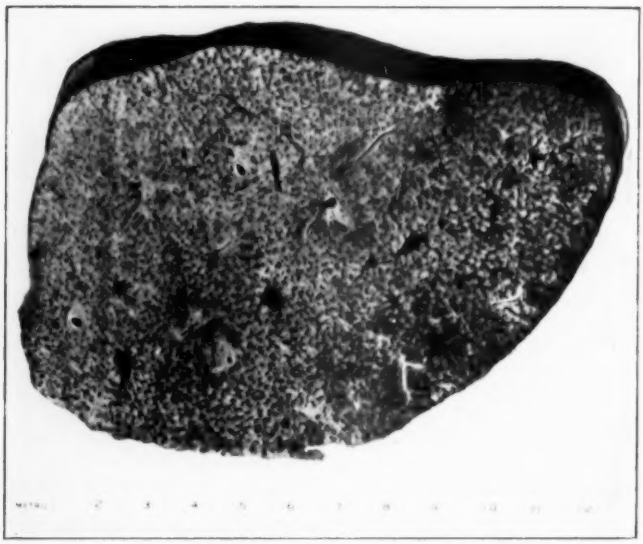

FIG. 4.—A section of the cut surface of the liver, showing the uniform tumor infiltration in the portal areas.

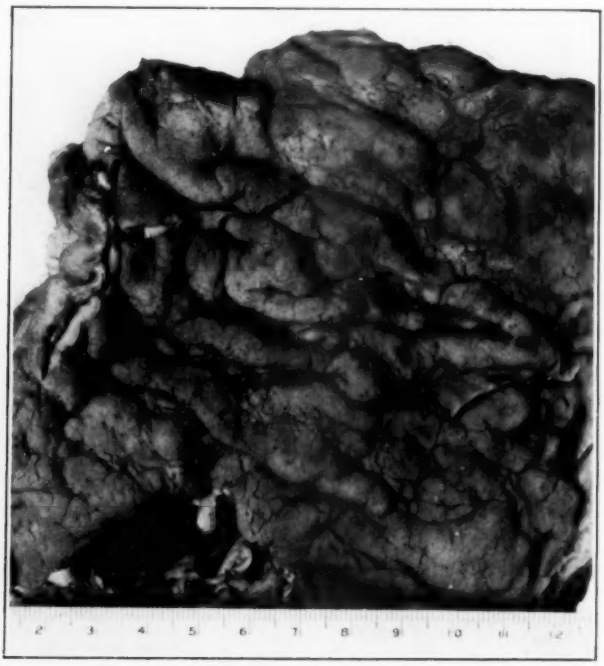

FIG. 6.—Stomach, showing the diffuse tumor involvement of the mucosa and submucosa. At one side of the picture a cut surface is shown.

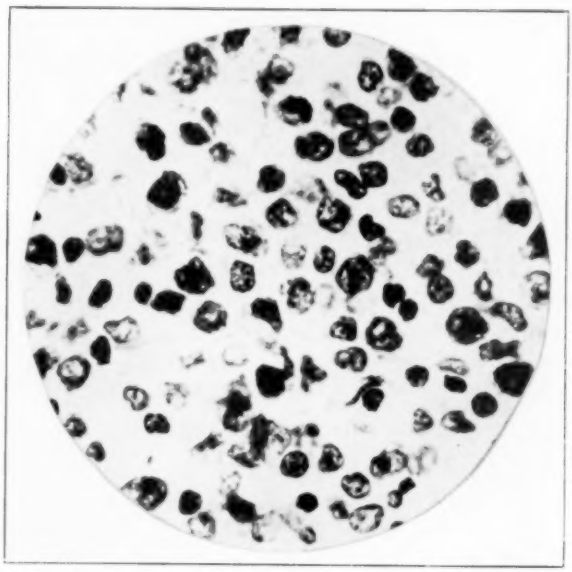

FIG. 7.—The large tumor cells in the portal areas of the liver. Mag. 650×.

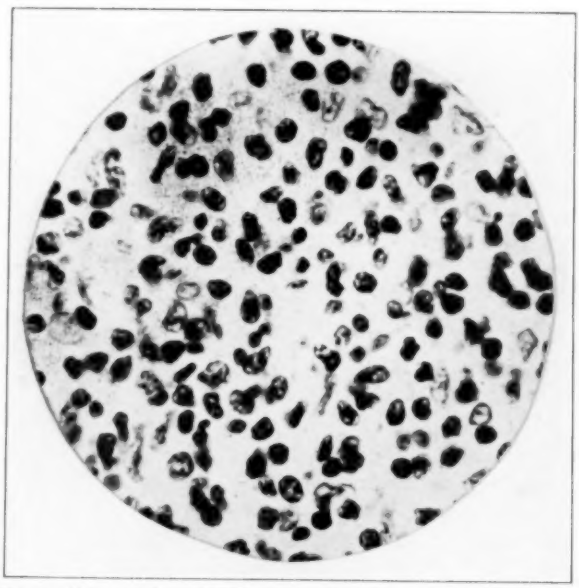

FIG. 8.—The small tumor lymphoid cells in a lymph node. Compare with Fig. 7. Mag. 650×.

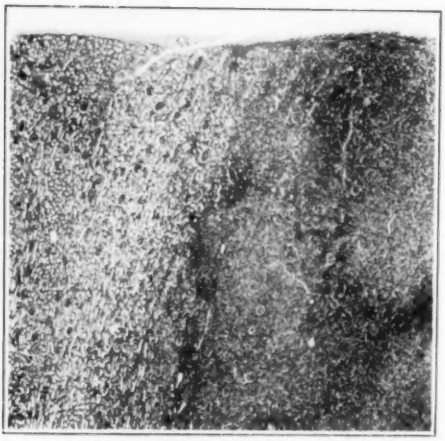

FIG. 9.—The tumor nodule in the kidney, showing the alternation of the lighter and darker zones of the tumor. The section is at the margin of the tumor and the adjacent kidney tissue. Mag. 10×.

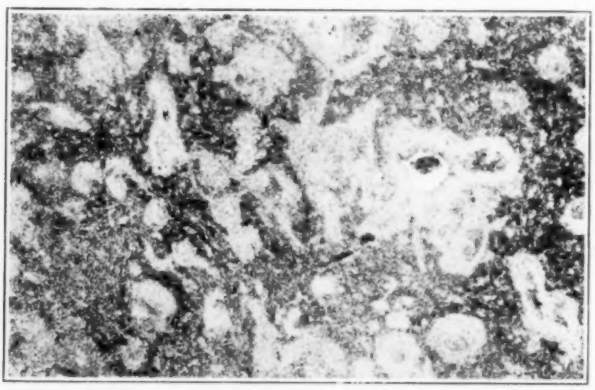

FIG. 10.—Spleen. This shows the tendency of the tumor to form more or less round lighter areas surrounded by darker areas. Mag. 10×.

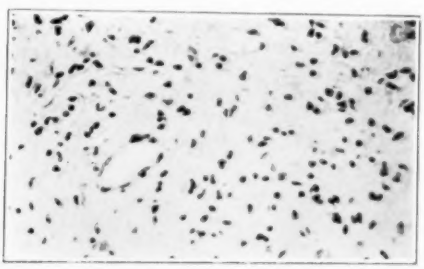

FIG. 11.—A retroperitoneal lymph node affected by the Roentgen rays, showing the marked diminution of lymphoid cells and increase of the fibrous stroma. Mag. 170×.

been replaced by tumor. There is marked infiltration of the tumor from 1 to 2 mm. beyond the original capsule, which in places has been replaced by the neoplasm. The lymphoid cells outside the capsule are less densely compact than those in the node. The cells have the same characters as in the tumor tissue found at autopsy and will be described later.

**Autopsy Findings.** The autopsy was performed on December 3, 1927, two hours postmortem, by Dr. D. H. Flashman.

*Chief Diagnoses.* Leukosarcomatosis, with primary lymphosarcoma of the retroperitoneal lymph nodes, and metastases to inguinal, mesenteric, gastric, mediastinal, axillary and cervical lymph nodes; heart; lungs; liver; spleen; kidneys; ureters; prostate; gall bladder; pancreas; suprarenal glands; stomach; duodenum; bone marrow of the right femur; thyroid; and blood (lymphatic leukemia). Lungs: Emphysema, atelectasis and healed apical tuberculosis. Liver, kidney, pancreas and suprarenals: Parenchymatous degeneration. Bone marrow of right tibia and lumbar vertebræ: Hyperplasia. Kidneys: Right—hydronephrosis, and chronic focal glomerulonephritis; left—hypertrophy.

*Anatomical Description.* The body is that of a well-developed, moderately emaciated white man, aged sixty years, and 172 cm. in length. *Skin:* There is a faint yellowish tinge generally, suggestive of slight jaundice. A few petechiæ are present beneath the left clavicle. Over the lower abdomen and upper part of the thighs there is a brownish pigmentation, probably from the Roentgen ray exposures. *Eyes:* The scleræ have a faint yellowish tint. *Mouth:* There are a few teeth missing and marked pyorrhea. *Peripheral lymph nodes:* On the left side of the neck above the clavicle there are felt 4 discrete glands 1 cm. in diameter. In the right axilla there are felt numerous discrete glands from 0.5 to 2 cm. in diameter, in all making a mass about 8 cm. in diameter. A few small nodes are felt in both inguinal and femoral regions in addition to a diffuse firm thickening.

*Internal Examination.* The subcutaneous fat is markedly atrophied. In the right axilla the lymph nodes are dissected out. There are about 30 nodes, from 0.5 to 2 cm. in diameter, all similar, discrete, and slightly firm (Fig. 2). Generally there is no appreciable invasion of the surrounding tissue, but in a few small areas there is slight invasion of the adjacent fat. The cut surface is slightly bulging, grayish-white, with small yellowish areas of necrosis in places, slightly soft, smooth or slightly granular, and moist. In the right inguinal and femoral regions there are about 8 lymph nodes from 0.5 to 1 cm. in diameter, surrounded by a diffuse infiltration of the tumor into the connective tissue, which appears quite fibrous. These nodes are much firmer than the axillary nodes and the cut surface is firm, slightly rough, fibrous, grayish-white, and not bulging. The fibrosis seems to be an effect of the Roentgen rays, since this region received the greatest exposure. A few similar but slightly larger nodes are also present in the left inguinal and femoral regions, and these do not show as much fibrosis as on the other side.

*Bone Marrow.* That of the right femur is examined for a length of 3 cm. at the midportion. It is uniformly grayish-white, soft, shiny and without fat. The marrow of the right tibia is yellowish and fatty for the most part, with portions slightly reddish, suggestive of red-cell hyperplasia; that of the lumbar vertebræ is moderately red.

*Abdominal Cavity.* The liver edge extends about 10 cm. below the costal margin. The diaphragm extends up on both sides to the third intercostal space. The posterior and lateral two-thirds of the spleen are firmly adherent to the chest wall, and the lower edge is 2 cm. above the costal margin. The mesentery shows throughout enlarged lymph nodes from 1 to 2 cm. in diameter, all discrete, firm, well encapsulated, and similar to those of the right axilla. All around the pancreas there are about 20 nodes of similar

character from 1 to 3 cm. in diameter. Beneath the peritoneal lining of the pelvis there is a diffuse uniform thickening of the posterior retroperitoneal tissues, averaging 2 to 3 cm. in thickness. It is most marked laterally, extending over the brim of the pelvis toward both groins, especially along the right femoral artery and vein. Except for a small plaque 5 mm. in diameter and 1 mm. thick, the peritoneal surface is perfectly smooth. Superficially the involvement of this tissue is not recognizable, but on incision the thickening is made out. This is composed of lymph nodes replaced by a firm, white, smooth, moist tumor tissue which infiltrates diffusely the surrounding connective tissue, where the tumor can be distinguished by its more opaque, pearly white, shiny appearance. These tumor areas are firmly adherent to the adjacent bone, connective tissue, muscle, and other

FIG. 3.—Cross-sections of the retroperitoneal tumor in the region of the aorta showing the firm nodes embedded in the diffuse infiltration of tumor.

structures. This involvement extends up over the vertebræ toward the diaphragm, varying in thickness about the aorta from 2 to 3 cm. laterally and about 1 cm. anteriorly and posteriorly (Fig. 3). In the region over the lower lumbar vertebræ and across the pelvis, the vena cava and iliac vessels are completely embedded in tumor which compresses and slightly infiltrates the wall of the veins, and in places small, whitish, firm thickenings of the intima are made out. When traced upward from the pelvic region the retroperitoneal lymph nodes along the vertebræ appear more and more discrete and there is less infiltration of the connective tissue about them. Both ureters are involved, more marked on the right and toward the kidney and bladder. They are surrounded by tumor tissue which infiltrates the wall and narrows the lumen, but does not project into the lumen, except for shallow plaques near the pelvis of the right kidney. The left suprarenal is firmly adherent at one pole to tumor tissue invading it from the retroperitoneal mass. It appears that the primary source of the tumor is in the retroperitoneal tissue in the region of the pelvis and in the right groin. Here

it has marked invasive tendency, but farther up, it gradually loses its local invasiveness and spreads extensively through the lymphatic system.

*Pleural Cavity.* There are a few slight adhesions at the left apex.

*Mediastinum.* There are about 4 nodes, 1 to 1.5 cm. in diameter, similar to those in the axilla. The thymic tissue is involuted and grossly free from tumor.

*Pericardial Cavity.* The heart is displaced slightly to the left, the right border being at the midline. Apparently this is due to the upward pressure of the liver. The pericardium over the aorta just above its origin shows tumor involvement, appearing as a pearly white, firm plaque about 4 cm. in diameter, 3 mm. thick in the center, and thinning out toward its irregular, indefinite margin.

*Heart.* It weighs 320 gm. It is essentially negative.

*Lungs.* The right lung weighs 400 gm. The left lung weighs 340 gm. They are slightly emphysematous, and in places at the bases slightly atelectatic. At the left apex there is a slightly retracted, fibrous scarring. The bronchial lymph nodes and the lung are not grossly involved with tumor.

*Liver.* It weighs 4570 gm. It is markedly enlarged, with rounded edges, and of slightly soft consistency. The external surface has a uniformly mottled appearance, with opaque, pearly white granules corresponding with the lobules. Near the midinferior border of the liver, the capsule has a patch of similar tumor tissue 1 to 2 cm. in diameter and 0.5 mm. thick. The ligaments of the liver show tumor infiltration. On section, the liver cuts with increased resistance. The cut surface is slightly rough with enlarged lobules throughout. Corresponding to the portal zones of the lobules there is a grayish-white, interlacing tumor infiltration. The central portions are reddish-brown. The connective tissue about the larger veins and ducts shows a diffuse, white tumor invasion for a width of 0.5 to 1 cm. (Fig. 4). The capsule of the liver over the gall bladder shows a dense tumor infiltration about 0.5 to 1 cm. in thickness, firmly adhering the gall bladder to the liver.

*Gall Bladder.* It is moderately distended with a thick black bile. The wall is infiltrated in patches 1 to 2 cm. in diameter and about 0.5 to 1 cm. in thickness. The mucosa is in places slightly rough and there are several shallow patches of polypoid projections of the mucosa overlying the areas involved with tumor. A few nodes similar to those in the mesentery are present about the hilus of the liver. The portal vein is negative.

*Spleen.* It weighs 830 gm., is markedly enlarged and of firm consistency. On the lateral surface there is a hyaline plaque of irregular shape about 7 cm. in diameter and 1 to 2 mm. in thickness. The capsule is thickened generally. On section the lymph nodules appear markedly enlarged throughout, and opaque, white granules of tumor can be made out generally. The cut surface is firm, smooth and moderately red. Streaks of fibrous tissue 1 to 2 cm. long and perpendicular to the surface are present beneath the hyaline plaque.

*Pancreas.* On the surface and in its substance there are numerous irregular pearly white, firm zones of tumor infiltration from 0.5 to 1.5 cm. in diameter (Fig. 5).

*Suprarenals.* Together they weight 8 to 9 gm. They are similar, having a narrow, deeply yellow cortex and a normal medulla. The surface of the left gland is invaded at one point by tumor from the surrounding tissues.

*Kidneys and Ureters.* The right kidney weighs 130 gm. It is of slightly increased resistance. The capsule strips readily leaving a slightly granular surface. On section, it cuts with increased resistance. The cortex in places is slightly narrowed, and the striations are quite irregular and indefinite. The medulla shows a few areas with yellowish amorphous precipitate. The pelvis is moderately distended and filled with abundant

similar precipitate. The lumen of the ureter in the first 5 to 6 cm. is markedly narrowed by the tumor involvement of the wall. The tissue about the pelvis shows a diffuse tumor involvement surrounding the vessels (Fig. 5). The left kidney weighs 240 gm. The cortex is 8 mm. wide. At one point in the cortex there is a white tumor nodule 2 cm. in diameter (Fig. 5). A few tiny opaque whitish dots suggestive of tumor are present in the cortex. The left ureter is not constricted as much as on the other side, but at the region just proximal to the bladder for a length of 2 cm. there is a marked accumulation of amorphous yellowish precipitate, some of which is embedded superficially in the lining.

*Gastrointestinal Tract.* The mucosa of the stomach (Fig. 6) shows markedly thickened folds and irregular projections throughout. On section there is diffuse, white tumor tissue infiltrating the submucosa chiefly, but in places also the mucosa and muscularis. The tumor areas are in places 1.5 cm. in thickness. There is some congestion and there are a few petechial hemorrhages, but no ulceration of the mucosa. In the duodenum and first

FIG. 5.—The larger piece of the kidney shows diffuse tumor infiltration in the region of the pelvic fat. The smaller piece of the kidney shows the circumscribed nodule found in the left kidney. The other two pieces show nodules of tumor in the pancreas.

portion of the jejunum, there are found in the submucosa small, similar tumor areas from 2 to 5 mm. in diameter. The remaining portion of the gastrointestinal tract is negative.

*Pelvic Organs.* The bladder wall is hypertrophied, but not involved by the neoplasm. The prostate is slightly enlarged, of normal consistency, and on section there are a few 0.5 cm. areas of hypertrophy with dilated glands. No tumor involvement is made out grossly.

*Thyroid.* It is not enlarged and a small piece is removed. It shows slight fibrosis, but no gross tumor.

*Aorta.* The lumen is slightly dilated and the wall is slightly thickened. Just above the aortic valve there is a whitish, shallow, atheromatous plaque about 1 cm. in diameter. A small amount of yellowish atheromata are scattered generally, more marked in the lumbar region where there are a few small ulcerated areas. Calcification is very slight in a few areas.

The brain and cord are not obtained.

*Microscopic Findings.* The tissue was fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin.

In the prostate, thyroid, heart, and lung small tumor areas are found which were not recognized grossly. Tumor areas are present in the sections of all the other organs where they were noted grossly.

In addition to the presence of the tumor the following changes are present in the sections of the various organs: The *heart* shows an occasional focus of fibrosis in the muscle and slight fibrous thickening of the intima of the coronary artery. In the *lung* are areas of atelectasis and of emphysema. The *liver* cells have some variation in the size of the nuclei and a uniform, finely vacuolar, swollen cytoplasm characteristic of hydropic degeneration and cloudy swelling. The liver cells adjacent to the tumor areas show compression atrophy. The epithelium of the bile ducts is hypertrophied. The cells in the central zones have slight pigment deposition and atrophy. In the *spleen* there is the thick hyaline capsule noted grossly, and beneath this there are areas of a rather loose fibrous structure and areas of hemorrhage. Slight hyaline degeneration of the arterioles is present. In the *left kidney* there is generally cloudy swelling and hydropic degeneration. An occasional fibrosed glomerulus surrounded by slight fibrosis and lymphoid cell infiltration is present, especially near the surface. There is atrophy of collecting tubules of the medulla and a rare hyaline cast. The *right kidney* shows near the surface many fibrosed glomeruli, surrounded by areas with atrophied tubules, fibrosis, and slight lymphoid cell infiltration. Similar but more marked degenerative changes are present as in the other kidney. The changes seem to be due to the hydronephrosis, since the medulla and collecting tubules show the greater amount of degeneration. The epithelium of the *ureter* is hyperplastic and hypertrophied, and the muscular wall is thickened. In the *pancreas* some of the islands of Langerhans have moderate hyperplasia and the cytoplasm of the acinal cells shows vacuolar degeneration. In the *thyroid* there is slight hyperplasia of the epithelial cells and in places tumor invasion is present between the follicles, compressing and replacing them. The *aorta* has in places a thickened intima with fatty material, fibrosis, and slight calcification. The media in places shows hyaline change and atrophy of cells. Very slight perivascular infiltration of lymphocytes with occasional plasma cells are found in the adventitia. The *bone marrow of the tibia* has in places marked hyperplasia due chiefly to red-cell formation; that of the femur shows only tumor.

*Character of the Tumor.* The tumor for the most part displays two main types of areas, those with chiefly large cells and those with chiefly small cells, but there occur many irregular variations of size and arrangement.

The tumor in the portal zones of the liver lobules serves as an example of the areas with larger cells (Fig. 7). Here the larger cells, which correspond to lymphoblasts, are found in greatest numbers. The nuclei average 5.8 $\mu$ in diameter and show numerous, usually atypical, mitotic figures. Rarely, several small nuclei are present in one cell. Compared with the small cells, the larger cells have a larger, less hyperchromatic, and more regular nucleus, a larger cytoplasm, and a less compact arrangement. Among these cells there are a few cells of the smaller type and of transitional types. In general both types appear to be more hyperchromatic than normal cells, and there is marked variation in size, shape and staining. Some of the nuclei have 1 to 3 large, basophilic nucleoli. A few karyorrhectic nuclei are present. The cytoplasm of the larger cells is small in amount, irregular in outline, finely vacuolar or granular, and acidophilic or basophilic. In some cells an eosinophilic, round body is present in the cytoplasm. Similar bodies, which seem to be of a degenerative nature, are also present between the cells. No evidence of a fibrous stroma formation is made out, but there is a fleecy, fibrinous exudate between the cells. An occasional red blood corpuscle and a rare eosinophil are present. A

few bile ducts with hypertrophied cells with vacuolar cytoplasm persist among the tumor cells. At the periphery of these tumor areas there is marked invasion of the adjacent sinusoids.

In the central portion of the liver lobules, away from the tumor areas, there is present in the sinusoids a marked increase in lymphoid cells similar to those in the vessels generally. These cells are smaller, more deeply staining, with very little cytoplasm, with irregular-shaped nucleus, and without mitotic figures. They resemble, but are not identical to, small lymphocytes. The average diameter of the nuclei of these cells is 4.4 $\mu$. The average diameter of normal lymphocytes in the tissues of a control case where the tissues were treated by the same technical processes is 4.3 $\mu$. The red blood corpuscles in the sections average 4.7 $\mu$. The proportion of tumor cells to red blood corpuscles in the capillaries is 1 to 3. The irregularity of the nucleus is most apparent on focusing up and down with the microscope. It does not seem to be due to shrinkage alone, as the other cells in the same sections do not have this character.

In the lymph nodes which have not been affected by the Roentgen rays, as in the original surgical specimen and the hyperplastic nodes of the axilla and other places, as well as in the nodule in the left kidney and in the spleen, the tumor shows a rather characteristic alternation of areas of large cells and small cells. This alternation often has a follicular arrangement with the larger cells in the center, corresponding to the appearance of germinal centers of normal lymph nodes (Figs. 1, 9 and 10). The larger cells resemble those in the tumor in the portal areas of the liver, while the smaller cells resemble those in the vessels generally (Fig. 8). This tendency to form follicular arrangements is not present in the sections of the bone marrow of the right femur, liver, gall bladder, stomach, lymph nodes only partially involved by tumor, and other places.

In those portions of lymph nodes and the spleen that are involved by the neoplasm there is obliteration of sinuses and normal landmarks. Infiltration beyond the capsule is more marked in the original surgical lymph node and the nodes of the retroperitoneal region than in the nodes which were more discrete grossly. The cells present in the diffusely invaded connective tissue and fat of the retroperitoneal region are in most sections chiefly the small and intermediate cells, mixed with a few cells of the larger type and here and there irregular foci of larger cells. In some sections the areas of large cells predominate.

The arrangement and combinations of these cells are very variable in different places. In the bone marrow of the femur the large type predominates with a few intermediate and smaller cells mixed among them. In the sections of the pancreas, stomach, and duodenum the cells are chiefly of the intermediate type. In the thyroid, lung, gall bladder, suprarenal, and prostate the large cell predominates. In the spleen the pulp spaces between the sinuses are filled with the small type of cell, suggesting that here is an important source of the small cells for the blood stream. Infiltration of vessels is also definitely taking place in the liver, bone marrow, and lymph nodes. In some lymph nodes the follicular areas of larger cells are composed of cells of an intermediate type. Mixed with the small tumor cells there are also some apparently normal lymphocytes, which are most numerous in the nodes that are least involved by tumor.

In areas of early involvement by the tumor a few mononuclear phagocytes and normal appearing lymphocytes are present and these are more numerous in areas of fat. Their presence seems best explained by the destruction of preëxisting tissue by the tumor. In the kidney there are small foci of small lymphoid cells about vessels and fibrosed glomeruli. Some of these lymphocytes appear normal, others appear like small tumor cells, and a few resemble the larger tumor cell. In lymph nodes with incomplete involvement por-

tions still show the preservation of the sinuses, which contain chiefly small tumor cells with a few larger ones, numerous mononuclear phagocytes, a few red cells, and some normal appearing lymphocytes. Some of the phagocytes contain from 1 to 3 well preserved, small tumor cells.

The tumor cells usually do not invade the media of large vessels, but in some of the iliac veins the infiltration extends through the intima. In one artery in the retroperitoneal tissue the vessel is invaded and thrombosed, with organization and canalization.

At one point in one of the retroperitoneal nodes there is an area of necrosis 3 mm. diameter. This appears to be in a focus of larger cells. The central portion shows some caseous necrosis. At the margin of this there are numerous mononuclear phagocytes and proliferating fibroblasts. In places there are groups of karyorrhectic necrotic cells, some of which appear to be large tumor cells and others phagocytes. Around the margin of these areas there are groups of large tumor cells which have not yet become necrotic mixed with others which have and some mononuclear phagocytes. The phagocytes in places resemble epithelioid cells, but there is no evidence of tuberculosis.

The retroperitoneal tissues, including the lymph nodes, ureters, veins, and prostate, show varying degrees of fibrosis and diminution of lymphocytes, apparently brought about by the Roentgen rays (Fig. 11). In some places there is no definite evidence of tumor, there remaining only connective tissue with scattered lymphocytes, most of which appear normal and tend to be smaller, darker, and more regular than those in the vessels. The average diameter of the nuclei of these cells is 3.4 $\mu$. In places foci of large or small cells still persist in varying degrees. The endothelial and connective tissue cells in these areas appear hypertrophied.

**Discussion.**—The autopsy presents a picture combining characters of lymphatic leukemia and lymphosarcoma and constituting a single type of involvement of intermediate character rather than a coincidence of two separate types. The involvement of the retroperitoneal tissues of the lower abdomen, pelvis and groins has the local infiltrative character of a lymphosarcoma, and appears to be an older lesion, as indicated by the more massive involvement and the clinical history. The more recent type of involvement of the lymph nodes elsewhere and of the liver, spleen, bone marrow, stomach and blood approaches, but does not attain the character of, a chronic lymphatic leukemia. The older and more recent types of lymph node involvement resemble each other in the presence of areas of large cells and of small cells in a rather characteristic formation. The older type, however, shows more invasion of the surrounding tissue. One can trace a gradual transition in the character of the lymphoid involvement in the retroperitoneal region along the lumbar vertebræ. Here there is a gradual loss of the infiltrative character of the tumor about the lymph nodes, going from the region of the pelvis toward the diaphragm. The circumscribed infiltrating processes in various organs, such as the kidney, pancreas, thyroid and prostate, appear like metastases of a lymphosarcoma, while the involvement of the liver, spleen, bone marrow and stomach approaches in character the diffuse distribution of a leukemia, but tends to retain the invasiveness of a lymphosarcoma. The involve-

ment of the lymphoid system is not universal as in typical lymphatic leukemia, but is much more extensive than in typical lymphosarcoma. The presence in the tissues of groups of large cells mixed with groups of small cells is likewise an intermediate characteristic in that it shows side by side two grades of differentiation of the tumor.

In the tissues there are both large and small tumor cells while in the blood practically only the small cell is found. Naturally, the small cell could more readily get into the vessels. However, the sections of the liver, lymph nodes, spleen and bone marrow show evidence of extensive invasion of bloodvessels not only by the smaller tumor cells but also by the larger cells. The relative absence of the larger cell in the blood suggests that in this case the larger cell tends to differentiate into a small cell in the blood stream. To be sure, many cases have been reported where the large cell is present both in the tissues and in the blood. But in this case, in the tissues the larger cells tend to differentiate into the small cell. This is shown by the presence of transitional forms and by the follicular arrangement of larger cells in the central portions surrounded by smaller cells, corresponding to the picture of a germinal center of a normal lymph node, where apparently the proliferating lymphoblasts differentiate to form the smaller lymphocytes which surround the germinal center and do not show evidence of division.

In 5 cases reported in the literature,[13,14,15] as in our own case, the development of the leukemia happened to follow Roentgen ray treatment. The rays in all of these cases apparently had a marked beneficial effect locally. In our case it produced clinically a marked diminution in the size of the glands, and histologically in places almost complete replacement of the tumor cells by a fibrous stroma. However, it apparently had no preventive effect on the development of metastases or of the leukemia. Evans and Leucutia[15] suggest that many cases of lymphosarcoma would develop leukemia if they lived long enough, as when life is prolonged by the Roentgen ray therapy.

Sternberg emphasized that the large lymphoblastic type of cell, which does not contain granules giving a positive oxidase reaction, was associated with his cases, and he believed this cell to be essential in these cases. In most cases of this type that have been reported, the large cell was present. In several cases of this type, however, the small cell predominated in the tissues and in the blood.[16,27–33] In other cases there were areas of large and of small cells in the tissues, and large cells in the blood.[10,12,16,26,34] In a few cases, as in our case, there were small cells in the blood and areas of large and of small cells in the tissues.[35,36,37] In a case reported by Graetz[31] in the tissues there were chiefly small cells, while in the blood early in the disease there were chiefly small cells and later chiefly large cells. It follows from this, as many observers have pointed out, that the term leukosarcoma cannot be restricted to cases having only large cells.

Similar combinations of local invasive tumors and leukemia occur in cases of myelogenous leukemia and especially in cases of chloroma, and for these Sternberg prefers to apply the term myeloleukosarcoma and chloromyeloleukosarcoma. Also there are cases which combine local tumors with aleukemic leukemias.

Objection has been made to this classification of tumors by Türk,[38] Herxheimer,[41] Fraenkel,[42] Herz,[40] Graetz,[31] and others. The discussion depends chiefly on whether this classification is a separate entity or simply a manifestation of infiltration of a leukemic process. In our opinion the arguments that have been presented are based on different points of view and too finely drawn distinctions. There have been reported all transitions between lymphosarcoma and lymphatic leukemia, so that it is obvious from the material available that no sharp line can be drawn between them, except for purposes of convenience. From this point of view, however, there is a class of cases which are intermediate in character between typical lymphosarcoma and lymphatic leukemia, and for these the term leukosarcoma may be used. Those who object to the term leukosarcoma suggest the term sarkoleukemia, but, as Paltauf[43] replies, this latter term does not indicate that the invasive process may be primary, as Sternberg and he believe often to be the case.

Ewing[44] points out that the neoplastic nature of the entire leukemic process has never received general endorsement, but in certain cases the picture varied from the standard type to a true neoplasm. He believes that these differences are best explained by different grades of hyperplasia. Cases of leukosarcoma, such as this one, bear out this idea in a striking way, by bridging the gap between typical leukemia and lymphosarcoma.

**Summary and Conclusions.**—A white man, aged sixty years, gave a history of a swelling in the right inguinal region for twelve months. A biospy showed lymphosarcoma. A roentgenogram revealed a tumor in his pelvis. The leukocyte count was normal. He was given Roentgen ray treatments for four to five months, during which time several examinations of the blood were negative. In the following month he developed a leukemia, the white blood count rapidly increasing to 444,000 cells per c.mm. at the time of death and the differential blood count showing 90 to 96 per cent small lymphocytes. The autopsy revealed a primary, invasive lymphosarcoma in the inguinal and retroperitoneal regions, an extensive involvement, resembling leukemia, of most of the lymphoid system, liver, spleen and bone marrow of the right femur, and metastatic nodules in most of the organs. In the tissues there were both large lymphoblasts and small lymphocytes, with intermediate types and in various combinations, indicating that these cells represent different degrees of hyperplasia or differentiation. The picture appears intermediate in character between typical lymphosarcoma and lymphatic leukemia, rather than a combination of two separate entities. The case falls in the group of leukosarcoma.

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## CHANGES IN THE EYE IN LEUKEMIA.*

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Since Liebreich (1861) published his original communication on 6 cases of leukemic retinitis, a number of other observations have been recorded on the retinal changes in leukemia. Most reports, however, have been based largely on individual cases. Leber has compiled an excellent summary of the changes in the eye in leukemia, and he has thoroughly reviewed the literature on the subject up to the year 1916. With reference to the frequency of such changes, he stated that, in the Tübingen Clinic, Mayer found retinal hemorrhages in 8 of 21 cases of leukemia during a period of sixteen years. Retinal changes are, however, more common in leukemia than this statement would indicate. Moore reviewed the changes in the eye

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in a group of 25 cases of leukemia observed personally. Retinal changes were present in 23 of the 25. He stated that few, if any, patients die of leukemia, whether lymphocytic or myelogenic, acute or chronic, without at some time showing ocular manifestations.

For the present study, complete clinical data including an ophthalmoscopic examination were available on 138 cases of leukemia. The patients were examined in the various sections on internal medicine in The Mayo Clinic and most of them were seen in consultation with specialists in diseases of the blood. The cases were grouped, on the basis of the diagnosis made by these consultants, into the acute and chronic myelogenous types and the acute and chronic lymphatic types. Seventy-nine of the cases were of the myelogenous type, 7 were of the acute and 72 were of the chronic. Fifty-nine of the cases were of the lymphatic type, 10 were of the acute and 49 were of the chronic. Eighty-nine of the entire group (65 per cent) showed retinal changes. Retinal changes were slightly more common in the acute than in the chronic cases and were more common in myelogenous than in lymphatic leukemia. Of the 17 cases of acute leukemia, 12 (70 per cent) showed retinal changes and of the 121 cases of chronic leukemia, 77 (63 per cent) showed retinal changes. Retinal changes were present in 63 (87 per cent) of the cases of chronic myelogenous leukemia; in 14 (29 per cent) of chronic lymphatic leukemia; in 6 (86 per cent) of acute myelogenous leukemia, and in 6 (60 per cent) of acute lymphatic leukemia (Table I).

TABLE I.—POSITIVE AND NEGATIVE FUNDI IN 138 CASES OF LEUKEMIA.

| | Number. | Positive. | Negative. |
|---|---|---|---|
| Acute leukemia | 17 | 12 | 5 |
| Myelogenous | 7 | 6 | 1 |
| Lymphatic | 10 | 6 | 4 |
| Chronic leukemia | 121 | 77 | 44 |
| Myelogenous | 72 | 63 | 9 |
| Lymphatic | 49 | 14 | 35 |
| Totals | 138 | 89 | 49 |

**Ophthalmoscopic Features of Retinal Lesions.** Both Leber and Moore divided the retinal changes found in leukemia into three distinct groups or stages (1) engorged veins or, according to Leber, simple inflammatory hyperemia; (2) engorged veins with hemorrhages, and (3) engorged veins with hemorrhages and definite leukemic infiltrations into the retina, true leukemic retinitis. Of Moore's 23 cases, 3 showed engorged veins, 16 engorged veins with hemorrhages, and 4 leukemic retinitis.

In our series of cases, besides those that could be placed in one or the other of the foregoing groups, there were some with hemorrhages without any noticeable engorgement of the veins, and others with retinitis indistinguishable from that of severe primary or secondary anemia. In 1 case, the retinal changes were indeterminate and

could not be classified. The remaining 88 cases arrange themselves, ophthalmoscopically, into five groups:

*Engorged Veins.* In 27 of 88 cases, the retinal veins were definitely engorged, but hemorrhage was not present. In some of these, the retinal arteries were also dilated.

*Engorged Veins with Hemorrhages or Exudates or Both.* In 35 of 88 cases, besides definitely engorged veins, various types of hemorrhage or exudate or both were present in the retina. The exudates, however, were of types not definitely recognizable as leukemic infiltrates. In some of these cases, the disks were full and blurred.

*Leukemic Retinitis.* In 10 cases, definite leukemic or leukocytic infiltration into the retina was present, particularly in the form of white lines sheathing the peripheral portions of the distended veins, but often also in the form of localized nodules with associated hemorrhages. In almost all of these cases, the disks were full and blurred and in some they were measurably swollen.

*Retinal Hemorrhages.* In 8 cases, hemorrhage was present in the retina; the retinal veins were not definitely engorged.

*Retinitis of Anemia.* Eight cases presented a type of retinitis which could not be distinguished ophthalmoscopically from that seen in cases of pernicious anemia or in cases of severe anemia, for example, secondary to carcinoma of the stomach or colon. The fundus in these cases showed definite anemia of the disk and of the blood columns in the retinal and choroidal vessels, usually some dilatation of the retinal vessels, both arteries and veins, scattered hemorrhages, and exudate of the superficial cotton-wool type (localized edema of the nerve fiber layer of the retina). The diagnosis of leukemia was established by the blood counts and other clinical features and was not suggested particularly by the retinal picture.

Many authors[2,4] stress the peculiar color of the fundus in leukemia. Supposedly it is due to the anemia combined with the excessive number of white cells in the circulation. According to one author,[2] it depends largely on leukemic infiltration of the choroid. As a matter of fact, the characteristic color is by no means always present and is seldom striking. The disks are usually pale and may be blurred, particularly at the margins. In some of the cases of leukemic retinitis, they are measurably swollen. Characteristically, the retinal veins are markedly distended and tortuous. Their caliber may be two to three or even four to five times that of the arteries and they often appear sausage-like. The arteries are, as a rule, of average normal caliber. They may be dilated and tortuous but never to the same degree as the veins. The pallor of the blood in the vessels is often striking. The veins are frequently rose-red and the arteries pale yellow. Grunert observed a distinct flow of blood in the dilated veins in a case of leukemia with choked disks.

Hemorrhages may be present in the retina either with or without other changes in the fundus. They vary greatly in number and

occur in all parts of the fundus. They may be round or irregularly shaped. They vary in color from very pale to deep red and in size from minute to disk size or larger. Infrequently they have a white halo. Hemorrhagic areas with a small distinct yellowish-white center are common. In a number of cases of acute leukemia, all of these areas were of the irregularly rounded type with more or less definite white centers. A large hemorrhage in front of the retina is sometimes seen, especially in the terminal stages of the disease.

The grayish-white patches, or exudates, in the retina, which are always less than a disk diameter in size, are of two varieties: deep nodules composed of leukocytes, and more superficial patches of varicose nerve fibers simulating the so-called cotton-wool exudates commonly seen in the vascular types of retinitis. The deep nodules are the more common and are characteristic of leukemia. They are usually round, sharply circumscribed, often elevated, and are often surrounded by a hemorrhagic margin. Usually, they are from one-sixth to one-third of a disk diameter but they may be two-thirds to three-fourths of a disk diameter. According to Bettmann, white patches may appear and disappear in a period of from twenty-four to forty-eight hours. He was, however, unable to determine to which of the two types the rapidly appearing and disappearing patches belonged. In true leukemic retinitis, the distended veins are often sheathed particularly in their peripheral portions, with white bands of varying widths. In connection with these perivenous infiltrates, large and often elevated masses of leukocytic infiltration into the retina may develop. In association with these masses, particularly at their margins, hemorrhagic areas are usually seen. When perivenous sheathing is present without much infiltration of the neighboring retina the underlying choroid often appears mottled, probably as the result of leukemic infiltration.

**Histologic Characteristics of Leukemic Retinal Lesions.** Leber has carefully reviewed the histologic studies of Bettmann, Bondi, Deutschmann, Kerschbaumer, Meller, Murakami and Roth in which leukemic retinal changes were observed during life. Hudson also gave an excellent summary of the histology of leukemic lesions of the eye. Parsons discussed the histologic data and the factors involved in their production. According to Leber the veins and capillaries are markedly dilated in the retina and the leukocytes within the vessels are markedly increased in number. In many cases, the lymph sheaths of the larger vessels are widened and filled with leukocytes; in some of the vessels the walls are infiltrated with leukocytes. Hemorrhages are present in the various layers of the retina, and also aggregations of leukocytes often surrounded by a ring of erythrocytes. Patches of gangliform hypertrophy of the nerve fibers may be present. Mild edema of the disk and retina is common. The optic nerve may be infiltrated with leukocytes. The retinal supporting tissue is often increased in amount.

The choroid is thickened due to dilatation of the blood vessels, particularly the veins, and at times by infiltration of the stroma with leukocytes. This diffuse infiltration of the choroid is apparently due to actual proliferation of extravasated immature leukocytes, since it has been found in cases in which the total number of leukocytes in the blood was not increased. It is usually seen in association with lymphoma of the orbit. Hudson considers the orbital lymphoma as the probable primary lesion, while Meller believes that it arises secondarily by extension from the choroid along the sheaths of the posterior ciliary arteries.

The nodular collections of leukocytes and the areas of gangliform hypertrophy of the nerve fibers found on histologic examination are seen ophthalmoscopically as white patches in the retina. It is difficult to differentiate them during life. The characteristic leukemic pallor of the fundus is dependent on the reduction of the hemoglobin and of the erythrocytes, on the relative and actual increase of the leukocytes in the retinal and choroidal vessels, and at times on the infiltration of the choroid with leukocytes. Deutschmann reported several cases showing the characteristic pale red without any infiltration of the stroma of the choroid. On the other hand, Meller reported a case with dense infiltration of the choroid in which the fundus during life had been of normal color, probably because of the deep pigmentation of the retinal pigment epithelium. It seems, therefore, that leukocytic infiltration of the choroid is a minor factor in the production of the characteristic pallor of the fundus.

The mode of production of the hemorrhagic areas and leukocytic infiltrates in the retina has not as yet been satisfactorily determined. Some authors, notably Verderame and Kerschbaumer, believe that they arise as the result of diapedesis of the blood through the poorly nourished walls of the vessels. According to Leber, supported in part by the observations of Murakami, they are always occasioned by direct escape of blood into the retina through actual rupture of the wall of the vessel following occlusion of the lumen by a mass of leukocytes and subsequent infiltration and softening of the wall. The peculiar characteristics of many of the hemorrhages with the large central collection of leukocytes are due, according to Öller and Murakami, to a tendency of the leukocytes to clump themselves together, or, according to Stock, to a separation of the erythrocytes from the leukocytes in the larger hemorrhages by sedimentation, or, according to Murakami and Meller, to actual proliferation of the leukocytes after their escape into the retina. The leukocytic areas of infiltration without hemorrhagic borders are probably, according to Leber and Murakami, ectasias of capillaries and small veins filled with leukocytes, and, as a result of diapedesis, surrounded by a sheath of leukocytes.

Since none of the eyes observed ophthalmoscopically in our

series was available for microscopic study we cannot offer anything original to the histology of retinal changes in leukemia.

**Clinical Significance of the Retinal Changes in Leukemia.** Little is found in the literature with regard to the factors influencing the occurrences of retinal changes in leukemia or with regard to the clinical significance of these changes with reference to the type, stage, future course or prognosis in leukemia. Leber stated that the occurrence of extensive hemorrhages in the eye indicates a general hemorrhagic disposition and the likelihood of the occurrence of hemorrhages in other parts of the body such as the subcutaneous tissues. Moore believes that the presence of retinal hemorrhages does not imply a more than usually grave prognosis. He stated that it is not rare to see a complete clearing of the fundus during temporary improvement in the patient's condition. He believes that the change in the composition of the blood affects the nutrition of the endothelium of the retinal vessels in such a way as to allow the escape of the fluid and cellular elements of the blood. Leber stated that the marked dilatation of the retinal vessels may be due to stasis induced by slowing of the blood stream. He does not believe that the type of leukocyte predominating is of any importance in the origin of the retinal changes. He believes that all the pathologic changes in the retina are due to the increase in leukocytes and to the circulatory disturbances produced by the changed composition of the blood. Andrewes and Rolleston suggested that a low platelet count may be a factor in causing retinal hemorrhages in acute lymphatic leukemia.

In view of the paucity of available data, we endeavored to determine the factors involved in the production of the retinal lesions, the stage and type of the disease in which they are most likely to occur, and their significance, particularly with reference to prognosis. If all the varieties of retinal lesions present in the different types of leukemia are considered in one group, it is immediately apparent that no one element of the changes in the blood can be held responsible for the retinal lesions, for changes in the fundus may be present when the leukocytes number as low as 4300, the erythrocytes are as numerous as 4,970,000 and the hemoglobin percentage as high as 75 (Dare). It is of interest also that the eyegrounds may be normal when the leukocytes number as high as 532,000, the erythrocytes as low as 1,440,000 and the hemoglobin percentage is as low as 18 (Dare). With this in view, and in order to make a more critical analysis of the available data, an attempt was made to consider separately each of the five types of retinal lesions in each of the four types of leukemia.

Retinitis of anemia occurred most frequently in acute myelogenous leukemia. The other types of retinal changes were present most often in chronic myelogenous leukemia. Engorged veins alone and engorged veins with hemorrhage and exudate were found

in all types of leukemia. Hemorrhage alone, without engorged veins, was found in all types with the exception of acute myelogenous leukemia. Characteristic changes in hemoglobin percentage, total erythrocytes or total leukocytes were not found to persist throughout the group of cases, showing engorged veins with or without hemorrhages and exudates or hemorrhages alone. The engorgement of the veins is sometimes due to the increased number of leukocytes. At other times, it is apparently a part of the dilatation of the vessels which usually occurs in severe anemia either as the result of lowered nutrition of the walls of the vessels or of lowered blood pressure. Hemorrhage into the retina either alone or in association with dilated veins is often the result of anemia and the resultant poor nutrition of the walls of the vessels. Sometimes the hemorrhage seems to occur as a part of a general hemorrhagic tendency. In these cases and also in others in which, near the terminal stage of the disease, they assume a purpuric form, the hemorrhages are often associated with a lowered platelet count. A definite relationship cannot, however, be established in general between the platelet count and the occurrence of retinal hemorrhages (Table II). The combination of engorged veins with hemorrhages

TABLE II.—RELATION OF PLATELET COUNT TO RETINAL HEMORRHAGES.

| Type of leukemia. | Without hemorrhages. | With hemorrhages. |
|---|---|---|
| Acute lymphatic | 20,000 to 54,000 (2 cases) | 20,000 to 280,000 (2 cases) |
| Acute myelogenous | .... | 68,000 to 320,000 (2 cases) |
| Chronic lymphatic | 60,000 to 310,000 (3 below 100,000) (6 above 100,000) | 54,000 to 280,000 (1 below 100,000) (2 above 100,000) |
| Chronic myelogenous | 88,000 to 780,000 ( 1 below 100,000) (13 above 100,000) | 84,000 to 1,022,000 ( 3 below 100,000) (11 above 100,000) |

and exudates is the most common retinal change in leukemia. The blood picture in cases presenting this type of retinitis is by no means uniform. In some cases the retinitis is probably due to the associated anemia. It is well known that anemia can cause the superficial type of cotton-wool exudate which is represented histologically by localized varicose hypertrophy of the nerve fibers. For the production of the nodular exudates typical of leukemia, however, actual leukocytic infiltration of the retina is necessary. As the total leukocyte count is not increased in some of these cases, the infiltration must depend on the invasive powers of the immature leukocytes rather than on the actual increase in their number.

Leukemic retinitis in its restricted sense with the characteristic leukemic infiltration into the retina, particularly along the veins, was found only in cases of chronic myelogenous leukemia. It was present in 10 of the 72 cases of this type. The infiltration was never

present except with a high total leukocyte count, the lowest count in the 10 cases being 45,300 and the highest 588,000. In all the cases of leukemic retinitis, the percentage of myelocytes and myeloblasts in the differential count was quite high. The percentage ranged from 16 to 60 and was below 30 in only 1 of the 10 cases (Table III).

TABLE III.—ACUTE MYELOGENOUS LEUKEMIA: TOTAL AND DIFFERENTIAL BLOOD COUNTS.

| | Negative (1 case). | Engorged veins (1 case). | Engorged veins with hemorrhage and exudate (1 case). | Retinitis of anemia (4 cases). |
|---|---|---|---|---|
| Range of leukocytes | 8,100 | 4,800 to 8,400 | 5,100 | 6,600 to 46,200 |
| Range of erythrocytes | 2,970,000 | 2,920,000 to 2,520,000 | 1,450,000 | 950,000 to 2,060,000 |
| Range of hemoglobin, per cent | 55 | 45 to 60 | 28 | 15 to 35 |
| Range of polymorphonuclears, per cent | 16 | 50 | 13 | 10 to 32 |
| Range of lymphocytes and lymphoblasts, per cent | 15 | 45 | 24 | 15 to 39 |
| Range of myelocytes and myeloblasts, per cent | 65 | .. | 53 | 19 to 73* |

* 3 above 30; 1 below 30.

In the 8 cases of leukemia presenting the ophthalmoscopic picture of retinitis of anemia, the changes in the blood were always those of secondary anemia of a rather severe grade. In these cases, the hemoglobin ranged from 15 to 40 per cent (Dare) and the erythrocytes from 950,000 to 2,600,000. This type of retinitis occurred in all the types of leukemia except the acute lymphatic type.

It is evident, then, that the type of retinal lesion found in cases of leukemia depends, to some extent at least, on variations in the blood picture. It is of interest also to consider separately each of the varieties of leukemia and to note in each the factors concerned with the onset of hemorrhagic and exudative lesions in the retina.

According to Vogel, and Ordway and Gorham, both varieties of acute leukemia present essentially the same clinical picture and run the same course. From the standpoint of retinal changes, they can be considered together. In the acute types of both lymphatic and myelogenous leukemia, the essential cause of the appearance of retinal lesions seems to be anemia. In these cases, as in pernicious anemia, it is rare to find retinitis when the hemoglobin is above 40 per cent (Dare) (Tables III and IV). That the tendency of the immature leukocytes to infiltrate the walls of the vessels and the tissues is also a factor in the production of the retinal lesions is

shown by the frequency of hemorrhagic areas with definite nodular white centers. A lowered platelet count may also be concerned in the causation of hemorrhages. In our series, however, hemorrhages were not always present when the platelet count was lowered.

TABLE IV.—ACUTE LYMPHATIC LEUKEMIA: TOTAL AND DIFFERENTIAL BLOOD COUNT.

| | Negative (4 cases). | Engorged veins (2 cases). | Engorged veins with hemorrhage and exudate (3 cases). | Hemorrhage only (1 case). |
|---|---|---|---|---|
| Range of leukocytes | 7,300 to 360,000 | 12,000 to 1,653,000 | 4,300 to 76,000 | 98,000 to 139,000 |
| Range of erythrocytes | 1,740,000 to 4,740,000 | 2,010,000 to 3,340,000 | 900,000 to 2,250,000 | 1,760,000 to 2,220,000 |
| Range of hemoglobin, per cent | 18 to 65 | 21 to 44 | 15 to 45 | 21 to 40 |
| Range of polymorphonuclears, per cent | 1 to 7 | 1.3 to 47.5 | 0.5 to 7 | |
| Range of lymphocytes and lymphoblasts, per cent | 90 to 97.5 | 47.5 to 98.7 | 88 to 99.5 | 99 |

In chronic myelogenous leukemia, the hemoglobin ranges definitely lower and the percentage of myelocytes in the differential count is definitely higher in the cases with retinal lesions than in those without them. It would appear that, except in retinitis of the anemic type, a high percentage of myelocytes and myeloblasts is the most essential feature for the production of retinitis, being much more significant than a high total leukocyte count (Table V).

In chronic lymphatic leukemia, the factors influencing the onset of retinal lesions seem rather less definite than in the other types. The most significant cause would seem to be the associated anemia. The percentage of lymphoblasts and lymphocytes in the differential count is more uniformly high in the cases with retinal lesions than in those without them, particularly in cases showing exudates in the retina. Since, however, definite infiltration into the retina along the veins was not noted in any of the cases, the relatively high percentage of lymphocytes must be of secondary importance in the production of retinitis. Some of the retinal exudates are probably lymphocytic infiltrations, but the tendency of the cells to invade the retina seems to be definitely less in lymphatic than in myelogenous leukemia (Table VI).

As previously reported by Wagener, ophthalmoscopic examination showed typical lipemic retinitis in a case of acute lymphatic leukemia. On analysis, the blood was found to contain 5 per cent total fats. The lipemia, which had developed coincident with a rather rapid fall in the hemoglobin percentage to 31 and of erythro-

TABLE V.—CHRONIC MYELOGENOUS LEUKEMIA: TOTAL AND DIFFERENTIAL BLOOD COUNTS.

| | Leukemic retinitis (10 cases). | Negative (9 cases). | Engorged veins (20 cases). | Engorged veins with hemorrhage and exudate (26 cases). | Hemorrhage only (5 cases). | Retinitis of anemia (2 cases). |
|---|---|---|---|---|---|---|
| Range of leukocytes | 45,300 to 588,000 | 19,200 to 378,000 | 12,900 to 545,000 | 9,500 to 575,000 | 149,000 to 317,000 | 17,300 to 32,500 |
| Range of erythrocytes | 2,120,000 to 3,910,000 | 3,330,000 to 4,680,000 | 1,500,000 to 4,810,000 | 1,850,000 to 4,460,000 | 2,550,000 to 3,890,000 | 2,090,000 to 2,220,000 |
| Range of hemoglobin, per cent | 30 to 60 | 53 to 78 | 28 to 69 | 23 to 75 | 42 to 60 | 37 to 40 |
| Range of polymorphonuclears, per cent | 30 to 56 | 48 to 70 | 6 to 70 | 13 to 65 | 30 to 64 | 42 (only 1 differential) |
| Range of lymphocytes and lymphoblasts, per cent | 1 to 4.5 | 0.5 to 15 | 0.5 to 85 | 0 to 47 | 1 to 7 | 5 |
| Range of myelocytes and myeloblasts, per cent | 16 to 60 (only 1 below 30) | 8 to 42 (only 1 above 30) | 6.5 to 45 (13 above 30) ( 7 below 30) | 0 to 70 (15 above 30) ( 8 below 30) | 32 to 45 (4 above 30) (none below 30) | 23 |

TABLE VI.—CHRONIC LYMPHATIC LEUKEMIA: TOTAL AND DIFFERENTIAL BLOOD COUNTS.

| | Negative (35 cases). | Engorged veins (4 cases). | Engorged veins with hemorrhage and exudate (5 cases). | Hemorrhage only (2 cases). | Retinitis of anemia (2 cases). |
|---|---|---|---|---|---|
| Range of leukocytes | 3,000 to 532,000 | 31,400 to 334,000 | 248,000 to 957,000 | 41,700 to 51,200 | 7,500 to 238,000 |
| Range of erythrocytes | 1,440,000 to 5,160,000 | 2,780,000 to 4,480,000 | 980,000 to 4,050,000 | 1,670,000 to 3,760,000 | 1,540,000 to 2,000,000 |
| Range of hemoglobin, per cent | 20 to 91 | 50 to 76 | 12 to 67 | 25 to 60 | 15 to 30 |
| Range of polymorphonuclears, per cent | 1 to 33 | 1 to 14 | 0 to 3.5 | 5.5 to 16 | 4 to 12 |
| Range of lymphocytes and lymphoblasts, per cent | 64 to 99 (20 below 90) (15 above 90) | 79 to 98 (2 below 90) (2 above 90) | 91 to 99 (all above 90) | 77 to 93 (1 above 90) (1 below 90) | 85 to 93 (1 below 90) (1 above 90) |
| Range of myelocytes and myeloblasts, per cent | 0 | 0 | 0 | 0 | 0 |

cytes to 1,000,000, disappeared with improvement in the blood picture following transfusion, the hemoglobin rising to 55 per cent and the erythrocytes to 3,340,000.

In lymphatic leukemia, the occurrence of retinal hemorrhages may be taken as indicative of a tendency to the occurrence of hemorrhages in other tissue; such as, the skin, subcutaneous tissues, and mucous membranes. In myelogenous leukemia, retinal hemorrhages do not seem to have the same significance with regard to hemorrhages elsewhere. Apparently, in myelogenous leukemia, hemorrhages occur in the retina much more frequently than in other tissues, while in lymphatic leukemia, the reverse is true. In acute myelogenous leukemia, petechiæ were present in the retina in 4 cases and in other tissues in 3. In chronic myelogenous leukemia, petechiæ were present in the retina in 45 cases and in other tissues in 9. In 4 other cases there was a history of hemorrhage in other parts of the body. In acute lymphatic leukemia petechiæ were present in the retina in 4 cases and in other tissues in 7. In chronic lymphatic leukemia, petechiæ were present in the retina in 9 cases and in other tissues in 10, and in 9 other cases there was a history of hemorrhage in other parts of the body.

There does not seem to be any definite stage of leukemia at which we can expect to find retinal lesions. Retinitis has been seen as early as three weeks after the onset of symptoms, and in the chronic cases normal fundi have been found as late as ten years after the onset of the disease.

In this series, the cases were not traced carefully over a sufficiently long period to make possible an exact determination of the prognostic value of the retinal changes in estimating the probable length of life of the patients. In the acute cases, the presence or absence of retinitis does not seem to furnish any index as to the length of life. It is of interest, however, that a marked increase in the size and number of hemorrhages into the retina was observed a few days before death in several cases of an acute or subacute form of the disease. In the chronic cases, retinal changes appear to be of some prognostic value. In chronic lymphatic leukemia, the average length of life after observation was two hundred and forty-eight days for the patients without retinitis and seventy-two days for the patients with retinitis. In chronic myelogenous leukemia the average length of life was ten hundred and thirty-nine days for the patients without retinitis and three hundred and fourteen days for the patients with retinitis (Table VII).

The effect of radium treatment of the leukemia on retinitis was carefully observed in only 1 case. This patient, a boy, aged eight years, entered the hospital June 24, 1926, with symptoms of three weeks' duration. A diagnosis of chronic myelogenous leukemia was made. On admission, the spleen was very large, extending below the level of the umbilicus; the hemoglobin was 30 per cent

Range of myelocytes and myeloblasts, per cent

(Dare), the erythrocytes numbered 2,550,000 and the leukocytes 588,000 of which 49 per cent were myelocytes and leukoblasts. At intervals of about seven days, radium was applied to the splenic area, a total of 19,400 mg. hours being given. His general condition improved considerably. At the end of the period of treatment, the spleen was only about a fourth of its original size, the hemoglobin was 45 per cent (Dare), the erythrocytes numbered 3,330,000, and the leukocytes 72,000, 34.5 per cent of which were myelocytes and leukoblasts. Before radium treatment was begun, ophthalmoscopic examination showed typical leukemic retinitis characterized by distinct edema of the disk and retina, tremendous engorgement of the veins and some dilatation of the arteries with a very pale, almost lipemic, appearance of the blood, numerous hemorrhagic and exudative areas in the retina, and definite leukocytic infiltration around the veins. Following treatment, the edema of the disk and retina almost disappeared, the dilatation of the veins was much less marked, the perivenous leukocytic infiltration was much less definite, and the number of hemorrhagic and exudative areas in the retina was considerably diminished.

TABLE VII.—COMPARISON OF LENGTH OF LIFE IN CASES WITH AND WITHOUT RETINITIS.

| Type of leukemia. | Shortest life, days. | | Longest life, days. | | Average life, days. | |
|---|---|---|---|---|---|---|
| | With retinitis. | Without retinitis. | With retinitis. | Without retinitis. | With retinitis. | Without retinitis. |
| Acute myelogenous | 4 | 34 | 64 | 34 | 35 | 34 |
| Acute lymphatic | 131 | 8 | 131 | 21 | 131 | 14 |
| Chronic myelogenous | 30 | 1039 | 1080 | 1039 | 314 | 1039 |
| Chronic lymphatic | 2 | 51 | 310 | 523 | 72 | 248 |

**External Ocular and Orbital Changes.**—External changes in the eye were infrequent in this group of leukemic cases. In 1 case of chronic myelogenous leukemia, slight ptosis of the upper lid was seen, in 2 cases slight inequality of the palpebral fissures, and in 1 case subconjunctival hemorrhage. In chronic lymphatic leukemia, edema of the lids was noted in 3 cases, subconjunctival hemorrhages in 4, and ecchymosis of the lids in 1. Ecchymosis of the lids was seen in 1 case of acute lymphatic leukemia. In 1 case of chronic lymphatic leukemia, at the time of the first examination the palpebral fissures were of unequal width and the accessory lacrymal glands were somewhat hypertrophied. A few months later, proptosis of the left eye developed probably due to lymphoma of the orbit.

Changes in the size and shape of the pupils and in their response to light and convergence seldom occur as the result of leukemia. When they do occur, they, like the narrowing of the palpebral

fissure and apparent ptosis previously noted, are probably due to pressure on the sympathetic nerves by enlarged cervical nodes. In one of our cases of chronic myelogenous leukemia, one pupil did not react to stimulation by light and contracted only slightly in convergence. A cause, aside from the leukemia, could not be found to account for the sluggish reflexes.

A history of blurred vision was given in only 8 of the cases of the series. Marked loss of vision was noted in only 2 cases. In one of these, vision was reduced to the ability to count fingers at half a meter and to six-thirtieths in the right and left eyes respectively, as the result of hemorrhage and exudates at the macula. In 1 case there was paracentral scotoma of one eye, due to a large hemorrhage near the macula. Gross defects in the peripheral fields of vision were not noted in the series.

**Summary and Conclusions.** In 138 cases of leukemia, retinal lesions were found in 70 per cent of the acute cases and in 63 per cent of the chronic cases, in 87 per cent of the myelogenous type and in 34 per cent of the lymphatic type.

The most common retinal picture in leukemia is that of engorged veins associated with hemorrhagic areas and with exudates of deep nodular or superficial cotton-wool type. It is found in acute and chronic cases of both lymphatic and myelogenous types.

The typical hemorrhagic area of acute leukemia is irregularly rounded with a nodular white center. When this type of hemorrhage occurs exclusively, or almost so, the diagnosis of acute leukemia is usually justified. Similar hemorrhages are found in association with the other retinal lesions in chronic leukemia.

Leukemic retinitis, showing, besides other lesions, definite leukocytic infiltration into the retina and choroid along the line of the retinal veins, was found in this series only in cases of chronic myelogenous leukemia. In all cases it was associated with a high leukocyte count and with a relatively high percentage of immature leukocytes in the blood.

In acute leukemia, the retinal lesions are due mainly to the anemia.

In chronic myelogenous leukemia, the main factors in the cause of retinal lesions are anemia and the high percentage in the blood of immature leukocytes of the myeloblastic type.

In chronic lymphatic leukemia, the main factor in causing the retinal lesions is the associated anemia. A high percentage of immature lymphocytes may be a factor in certain cases.

In myelogenous leukemia, hemorrhage in the retina is more common than in the skin, subcutaneous tissues, and mucous membranes. In lymphatic leukemia the reverse is true.

Retinal lesions may be seen in leukemia as early as three weeks after the onset of symptoms, and a normal fundus may be found as late as ten years after the initial symptoms of the disease.

In chronic leukemia the average subsequent length of life was

considerably less in cases with retinal lesions than in those with a normal fundus at the time of the first examination.

In one case of chronic leukemia marked improvement in the retinal lesions and considerable improvement in the general physical condition followed radium treatment.

Infiltration of the lids and orbit and subconjunctival ecchymosis and ecchymosis of the lids are relatively infrequent in leukemia.

Pupillary and visual field changes as a result of leukemia are rare.

Definite reduction of vision was present in only 8 per cent of the cases of leukemia.

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## ON THE GENERALIZED EFFECT OF RADIATIONS IN MYELOGENOUS LEUKEMIA.

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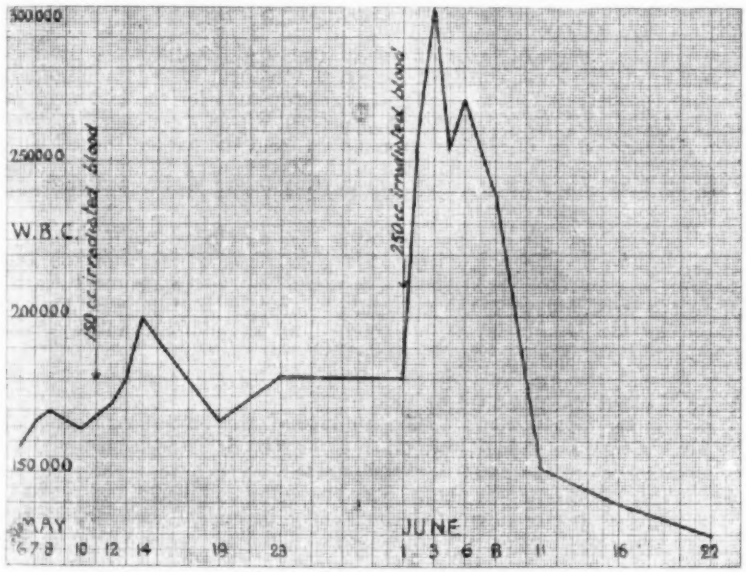
In a previous paper[1] on the effect of radium applications on the morphology of the blood in myelogenous leukemia, the following conclusion was reached: "The mechanism of action of radium upon the leukemic foci is of a generalized as well as localized nature." In other words, when radium is applied to any portion of the body, its effect is carried by the blood stream to the leukopoietic foci. Thus, from a local application, a generalized action is obtained. The purpose of the present paper is to present definite evidence in

support of this view, using the clinical material of 2 cases of myelogenous leukemia, treated with the rays.

**Case Reports.** CASE I.—Mrs. E. W., aged thirty-two years, housewife, was admitted to the Misericordia Hospital on May 4, 1927. The patient stated that about a year before admission she first had a sensation of weight on the left upper side of the abdomen. Later she was able to palpate there a mass, which grew steadily in size. The patient did not lose weight, and had no serious disturbance except for slight loss of strength.

Upon admission, the patient appeared pale but in fair condition of nourishment. The left side of the abdomen was bulging and on palpation a hard mass was found which reached from the costal margin down the crest of the iliac bone. The lateral limits of the mass were the left lateral sternal line and the left anterior axillary line. The urine contained a cloud of




CASE I.—Effect of autotransfusion of irradiated blood on the leukocyte count in a case of myelogenous leukemia.

albumin. The blood urea was 13 mg.; creatinin, 1.8 mg.; uric acid, 3.4 mg. per cent. The basal metabolic rate was + 32 (Harris and Benedict standard). The blood-coagulation time was four and a half minutes, the bleeding time fifteen minutes. The hemoglobin content was 12.8 gm. per cent; the erythrocytes were 3,230,000; the leukocytes 158,400. The differential count was: hemocytoblasts, 6.5 per cent; myeloblasts, 3 per cent; promyelocytes, 11.5 per cent; myelocytes, 13 per cent; metamyelocytes, 9 per cent; neutrophilic polymorphonuclears, 44.5 per cent; eosinophils, 4 per cent; mast cells, 6 per cent; lymphocytes, 2.5 per cent; normoblasts, 2 per cent.

The diagnosis of myelogenous leukemia was made. For a week from the day of admission, daily complete blood counts were made to determine the fluctuation of the number of cells. The patient did not receive, during the period of observation, any drug or therapeutic treatment, except those here reported.

The average number of leukocytes per cu.mm. for the week ending May 11, was 165,320, and the maximum variations were within 4.4 per cent.

On the morning of May 11, 150 cc. of blood were removed by venesection, mixed with sodium citrate solution in a sterile Pyrex beaker, covered with a thin layer of gauze. This was immediately irradiated, with 10 per cent of an erythema dose of filtered rays.

Within ten minutes from the time of removal, the blood was reinjected into the patient. There was no reaction following this procedure, except a very slight chill in the afternoon. Twenty-four hours later, the leukocytes were 172,000; two days later, 181,000; three days later, 200,000. In eight days they were back within the limits established before. The temperature fluctuated from 98° to 100° F. with daily elevations; the pulse from 76 to 110; respirations were 24.

Uric acid rose to 8.2 on May 20. Oozing of blood occurred from the venesection wound, and lasted until May 21. The coagulation time was four minutes, but the bleeding time was a little over fifteen minutes. The platelets were 300,000 per cu.mm.

On May 23, a perceptible diminution in the size of the spleen was noticed.

On May 30, the lower border of the spleen was 4 cm. above the umbilical line and the patient felt well. The leukocyte count for the last week of May had averaged 180,500, with variations well within 2 per cent.

On June 1, 250 cc. of blood were removed from the patient, mixed with sodium citrate solution and irradiated, with 20 per cent of an erythema dose of filtered rays, and reinjected into the patient within fifteen minutes from the time of removal.

The patient had no reaction following the autotransfusion. Twenty-four hours after the injection of irradiated blood the leukocytes were 258,000; two days later 300,000. Free bleeding occurred from the phlebotomy wound during the week following the autotransfusions; on the night of June 3, the patient lost about 500 cc. of blood. The coagulation time was five minutes, but the bleeding time was extended over one hour.

On June 4, the uric acid in the blood was 12 mg. per cent. Slight oozing of blood continued up to June 6.

The number of leukocytes slowly diminished and on June 22, without any further treatment, they were down to 130,000 or 22 per cent less than the average before the treatment was started. The lower border of the spleen on the same date was about 4 cm. above the umbilicus.

The changes in the differential count may be summarized as follows: The primordial cells before the treatment were 6.5 per cent and the immature cells of the granulocytic series 33 per cent. Forty-eight hours after the first autotransfusion of radiated blood, the primordial cells rose to 9 per cent and the immature cells of the granulocytic series to 41 per cent. There was also a distinct increase in the number of lymphocytes, and megaloblasts, previously absent, made their appearance in the circulating blood. Similar changes occurred after the second autotransfusion.

**Summary of Case I.** A young white woman, with an early untreated myelogenous leukemia received two autotransfusions of irradiated blood. After each one of the transfusions, blood changes occurred, in all respects similar to those obtained where radiations are applied to the body (long bones). A marked diminution of the spleen was also obtained.

CASE II.—J. M., an adult Negro, aged forty-five years, laborer, was admitted to the Philadelphia General Hospital, September 1, 1925. The patient had had smallpox, typhoid fever, malaria, syphilis and gonorrhea. About sixteen months before admission, he first complained of weakness accompanied by rise of temperature. Three months before admission, the

patient noticed an enlargement of the abdomen and swelling of the legs. On admission, there were signs of fluid in both thoracic cavities below the fourth rib; a double murmur could be heard over the aortic area of the heart; there was moderate ascites, enlarged liver, and enlarged spleen. The latter reached down below the crest of the iliac bone, and to the right the umbilical line. The lower extremities and scrotum were edematous. Dyspnea was present throughout his short stay in the hospital. The temperature varied from 96° to 100° F., the pulse from 80 to 100, and respiration from 20 to 30.

The blood examination, done on admission gave the following result: hemoglobin, 47 per cent; erythrocytes, 2,507,000; leukocytes, 153,000. The differential count showed 57 per cent of immature granulocytic cells, and 35 per cent of neutrophilic polymorphonuclears. A diagnosis of myelogenous leukemia and syphilitic aortitis, with regurgitation, was made.

A paracentesis was performed; the puncture wound oozed a small amount of blood up to the end. A first radium application was given on September 4 over the sole of the left foot, the left internal malleolus, and the lower third of the left leg. On September 5, the leukocytes rose to 291,000 at 9 A.M. That afternoon at 2 o'clock, they were 298,000.

The following day, another radium application was given, over the sole of the right foot, the right internal malleolus, and the lower third of the right leg. On September 6, at 10 A.M. the leukocytes were 103,000. The patient died at 2.30 P.M. the same day from rapidly progressive cardiac decompensation.

The changes in the differential counts can be briefly summarized as a marked increase in the number of the primordial cells (from 14 per cent to 28 per cent) and the appearance of megaloblastic cells. Such changes have been previously found to be a feature of first radium application.[1]

Autopsy was performed twenty-four hours after death. Myeloid infiltration of all organs was the outstanding feature. The spleen weighed 3400 gm. and liver 4850 gm. There was a typical syphilitic aortitis with retraction of the valvular leaflets, and the liver showed gummas.

Particular attention was paid to the bone marrow, with the following results: the bone marrow of both tibiæ, upper and lower portions, was yellow, fatty and contained spongy bone. It appeared altogether as nonfunctioning adult bone marrow. The marrow of the bones of both feet was identical in structure and appearance with the bone marrow of the tibia. The bone marrow of the femur and of the sternum was red and gelatinous with few hemorrhagic points. From all of these portions of the bone marrow, smears were made, also paraffin sections that were stained with May-Gruenwald-Giemsa, according to Pappenheim's method, and frozen sections, which were stained with the oxidase stain.[2] The results of the examinations were as follows:

| | |
|---|---|
| Upper tibia (nonradiated)<br>Lower tibia (radiated)<br>The bones of the foot (radiated) | Numerous bony spicules are scattered throughout the fatty marrow with few cells grouped in small foci; no fibrosis; no degenerative changes. The few cells found resemble those of the bone marrow of the femur; the differential count being comparable with that obtained on smears from the femur; about 70 per cent of cells contain oxidase granules. |
| Femur (sections from several portions)<br>Sternum | Numerous granulocytic cells, mature, immature, and pathological. Numerous immature and embryonic cells of the erythroblastic series. Seventy per cent of the cells contain oxidase granules. |

Aplastic bone marrow in the tibia accompanied by hyperplastic changes in other bones has been observed by the author in a long series of cases including all forms of anemia, acute and chronic leukemia, and acute and chronic inflammatory processes, especially sepsis, accompanied by profound changes of the blood picture. It appears therefore, that the bone marrow of the tibia is a poor index of the general conditions of the bone marrow. Since the bone marrow of the tibia is readily accessible, it has been often depended upon at autopsies to indicate the general condition of the bone-marrow; a practice which should be discontinued.

**Summary of Case II.** An adult Negro with advanced myelogenous leukemia was given two radium treatments on consecutive days, the emanation tubes being applied over the lower third of both tibiæ and the short bones of both feet. That the application had effect was evidenced by the sudden rise in the number of leukocytes, followed later by a sharp drop, and by the conspicuous changes in the differential blood count. At autopsy, it was found that there was no hyperplastic bone marrow in either tibia, nor in the short bones of the feet, but only fatty aplastic bone marrow; also that there was no difference whatever, between the bone marrow of the bones which had been radiated, and of some that had not been radiated. This was especially evident, comparing smears and sections of the lower third of the tibia, radiated, and the upper third of the tibia, which had not been radiated.

**Discussion.** In the first of the cases presented, it is obvious that the radiations as such or their effects were carried by the whole blood irradiated.

In the second, it would be very difficult to trace a direct effect of the radium applications upon the bone marrow of the bones irradiated. The effect of the radium emanations upon the hemoplastic foci must be explained on the ground that the radium emanations as such are carried by the blood or that they act through the production of leukotoxins, which are produced by the direct effect of the radium emanations upon the white cells of the blood in superficial vessels, or perhaps upon fixed cells of the reticuloendothelial system.

In fact, in the second case, there was *no active* bone marrow in the bones radiated, and there was no difference between the portions irradiated, and those *not* irradiated.

The literature[1] on the subject of the application and possible mechanism of action of radiations in chronic myelogenous leukemia, shows a great disparity of views among workers as to the best place to apply radiations in treating myelogenous leukemia. This observation, and the fact that regardless of the place of application very similar results are obtained, lends support to the view that the direct action of radiations upon the hemopoietic foci is altogether unimportant. In all cases the blood acts as carrier of radiations, either as such or modified, to the hemopoietic foci, where its main action takes place. A very interesting observation was made by Kotzareff

and Weyl:[3] they found that the intravenous injection of autoserum charged with emanations results in the fixation of the emanations by embryonic or neoplastic cells. We have not been able to find whether or not such observations have been confirmed. Should they be, aside from their practical importance in the diagnosis and treatment of malignant growth, they would greatly aid in settling the question of the mechanism of action of radiations on leukemia. At present, experimental work on animals is being carried on to throw new light on the question.

**Conclusions.** Radium and Roentgen ray affect the hemopoietic centers by an indirect generalized action rather than by a direct local effect. It is not yet clear whether this indirect effect is produced by the blood transfer of emanations to the bone marrow, or by the extramedullary production of leukotoxins, which are then transported to the bone marrow.

In the treatment of myelogenous leukemia by radium or Roentgen ray it is the dosage rather than the place of application that is important.

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## INFECTION AS A CAUSE OF JUVENILE CIRRHOSIS.*

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Cirrhosis has no definite age period of occurrence; cases occurring in infants are not rare. Mackay[11] reports a case beginning in a babe aged eleven days and ending fatally twenty-seven days later. Abt[2] records a case beginning at two weeks of age and progressing to a fatal termination five months later. Postmortem examination confirmed the diagnosis in each case. It appears that cirrhosis in the newborn is rare, and that the frequency of occurrence increases with age. Seitz[14] summarizing 320 cases, found 31 among sucklings, 72 in young children and 217 in children of school age. Among these were occasional instances in which several children in the same family died of cirrhosis.

* The experimental work reported here was made possible through funds from the Martin Research Foundation.

Cirrhosis occurring in the young presents certain important differences from that seen in adults. Marked enlargement of the spleen is an early and almost constant feature. I have collected data from several hundred reported cases: marked splenic enlargement has been an associated feature in more than 90 per cent. The spleen is often of huge dimensions approximating those found in leukemia. Concurrent with the enlargement of spleen and liver, anemia of gradual onset is usual. Cirrhosis in children occurs in the same general forms as in adults, but cirrhosis of the biliary type occurs more frequently than in adults. The occurrence of intermediate or mixed forms is very frequent. This discussion will be limited to those forms, often designated as hypertrophic and atrophic, which are analogous to the portal cirrhosis of adults. It is understood that the term hypertrophic is often assigned because of the increased size of the liver. Such increase in size is a regular feature of the early stages of the process which ends in the typical "hob-nailed liver" of atrophic or portal cirrhosis. This form of enlarged liver occurs very frequently in children, and the designation hypertrophic cirrhosis does not necessarily imply a different form of disease. Cirrhosis in children is more acute and runs a more rapid course than in adults.

Many pathologists[17] discuss cirrhosis as chronic hepatitis. This conception contributes to a clearer understanding of the process, since hepatitis implies inflammation-reaction to injury which may be the result of diverse causes. Hepatitis properly includes the cellular degeneration and fatty changes, resulting in increased size of the organ—hypertrophy—in the early stages. It includes the cellular destruction, and the resulting active proliferation of both liver cells and bile ducts. It includes the infiltration with inflammatory cells, and the reparative proliferation of fibrous tissue, the contraction of which results in the decreased size—atrophy—of the later stages.

The assembled evidence indicates that juvenile and adult cirrhosis do not differ in etiology. In case reports of juvenile cirrhosis the causative agents most frequently assigned are alcohol, vaguely defined intoxications, congenital anomalies and infections.

If alcohol were the chief primary cause, the condition should occur in a much higher percentage among those addicted to its use than among nonusers. A drug capable of producing such change should have a demonstrable toxicologic action, as do mercuric chlorid, phosphorus, chloroform, or other drugs whose effects can be shown readily by experiments on animals. Cirrhosis has not followed the use of alcohol experimentally. This fact, together with the frequent occurrence of cirrhosis in those having no alcoholic history and its relative infrequent occurrence in alcoholic habitues, indicates the importance of other factors than alcohol. Adami[3] commented on the failure of alcohol to produce characteristic cirrhosis in animals

and stated that "extreme cirrhosis may attack children and adults who have never taken a particle of alcohol either medicinally or otherwise." Excessive use of alcohol produces fatty infiltration of the liver in man and in animals. In this connection, the experiments of Opie[15] are significant. He was able to produce cirrhosis in animals by first causing degeneration of the liver by the administration of chloroform, then inoculating living bacteria intravenously. Streptococci were used in some of his experiments; in others Bacillus coli was used. He believed the chloroform acted to lower the resistance of the liver rendering it subject to the infection. He suggested the possibility that alcohol may play a rôle similar to that of chloroform in these experiments. The combined action of two factors, as lowered local resistance resulting from injury by alcohol, chloroform or other agents, plus bacterial infection, has received less attention than it seems to merit.

Space does not permit a review of the evidence on toxic cirrhosis. Its importance is generally recognized and has been substantiated by experiments on animals. A number of injurious substances, quite diverse in character, have been used to produce cirrhosis more or less closely resembling that occurring in man.

That congenital abnormalities may occasionally be of such kind as to result in cirrhosis is admitted. There is evidence that this cause is frequently assigned when cirrhosis of unknown origin would be a proper diagnosis. Cirrhosis due to congenital abnormalities is seldom verified by postmortem examination.

Infection is frequently mentioned among etiologic factors. In his summary of 320 cases, Seitz stated that about 33 per cent were of infectious origin. Supporting this view is the frequent occurrence of fever, malaise, nausea, rapid pulse and other evidences of infection. Leukocytosis is present in a considerable proportion of cases. When the leukocytes are not increased, a leukopenia is usually present. The splenic enlargement and anemia which mark the early stages of cirrhosis could be produced by a chronic infection as readily as by toxic agents. The histologic alterations present resemble those of a chronic infection. The leukocytic infiltration, and the active reparative processes seen in rapidly developing cirrhosis are typically the reaction called forth by chronic infection. Syphilis, kala azar and other tropical infections may produce cirrhotic changes indistinguishable from the type under discussion. The demonstration of the parasites in the liver substance in these diseases is accepted as evidence of the causative agent. That other infections than those mentioned may produce a similar result is probable.

Bingel[5] made examinations of the livers in fatal cases of scarlet fever. In each case he noted extreme degeneration and necrosis of the liver cells and inflammatory infiltration about the vessels. In the liver of a case in which death followed a protracted attack

of scarlet fever he found those same changes present, but in addition there was the rapidly proliferating fibrous tissue which characterizes early cirrhosis. He regarded the fibrous proliferation as an attempt to repair the injury resulting from the infection. Several writers comment on the occurrence of cirrhosis following scarlet fever and measles.

In a case reported by Mya,[13] cirrhosis developed during the course of a prolonged enteritis. At postmortem examination chronic ulceration enteritis was found, and cirrhosis of atrophic type. Others comment on the development of cirrhosis during the course of chronic infections such as bronchitis, pleuritis, meningitis, arthritis and endocarditis. Edwards[7] in a review of 100 cases found an active associated infection in 25 per cent of them.

Bolton[6] reported a case of cirrhosis in a child in which the postmortem examination showed a purulent peritonitis without apparent cause. He believed the cirrhosis was produced by infection of the liver, which finally spread to the peritoneal surfaces. In cases of cirrhosis an associated pleuritis, pericarditis or peritonitis is often found at postmortem and the occurrence of inflammatory adhesions about the liver and spleen is particularly frequent. These suggest infection rather than intoxication with chemical or metabolic products.

Levi,[10] in 1898, reported a case in which cirrhosis was concurrent with mitral endocarditis in a boy, aged seventeen years. He cultivated from the liver a diplococcus which was pathogenic to guinea pigs.

Adami[3] investigated an epidemic disease of cattle of which cirrhosis, resembling that occurring in man, was the prominent pathologic feature. He found minute coccoid bacilli in the livers in great numbers. When cultivated, this organism resembled somewhat the bacillus of hemorrhagic septicemia. When injected into rabbits the infection localized in the liver, producing degeneration and necrosis of liver cells. The rabbits died before cirrhotic changes had time to develop. Having established the infectious nature of cirrhosis in cattle, Adami and Abbott[1] used the same methods in human cases. By special staining methods they demonstrated great numbers of organisms in the livers of 5 human cases, and cultivated the organism in 4 cases. This organism was very minute, ovoid or coccoid in shape and grew in long chains. It manifested a confusing pleomorphism, but was identified as a strain of Bacillus coli by Adami's coworkers. On the strength of these findings, cirrhosis is discussed as an example of the mechanism called subinfection in Adami's volume on *General Pathology*.

Mallory[12] examined for bacteria the livers from 2 cases of juvenile cirrhosis and found slender bacilli, possibly Bacillus coli, in 1 of them. No cultures were made. He believed these cases were of infectious origin.

FIG. 1.—Case I. Juvenile cirrhosis, photograph of liver and spleen.

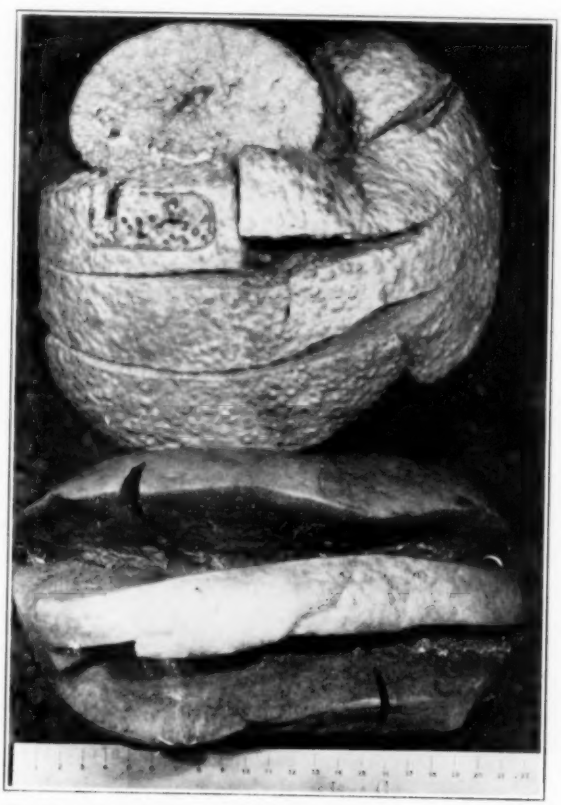

FIG. 2.—Case II. Juvenile cirrhosis, photograph of liver and spleen.

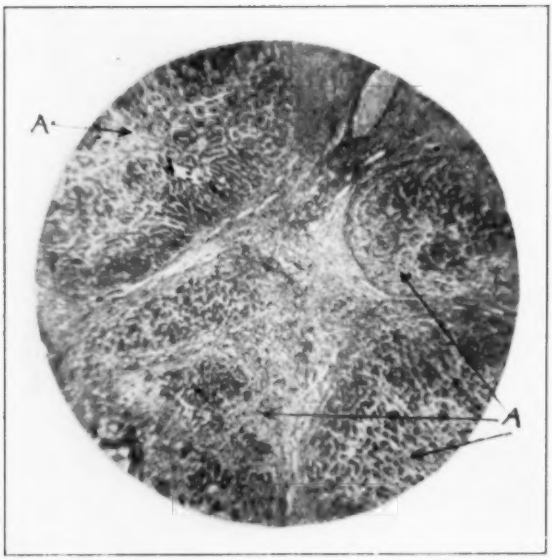


FIG. 3.—Case II. Liver, low magnification. Shows perilobular distribution of mature fibrous tissue. New fibrous tissue invading lobules where destruction of liver cells has occurred, as at *A*.

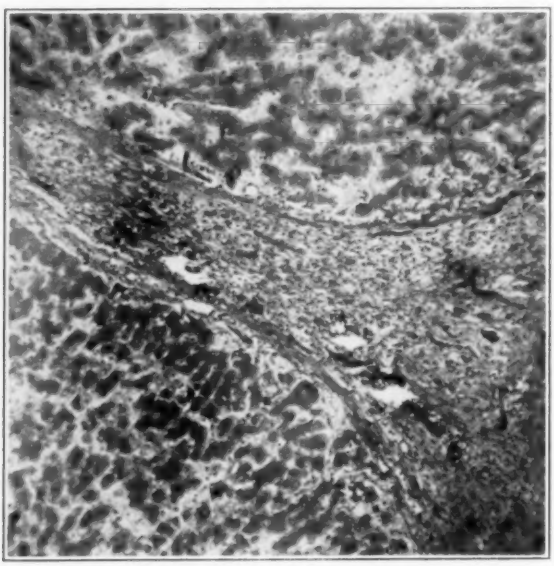

FIG. 4.—Case II. Liver, medium magnification.

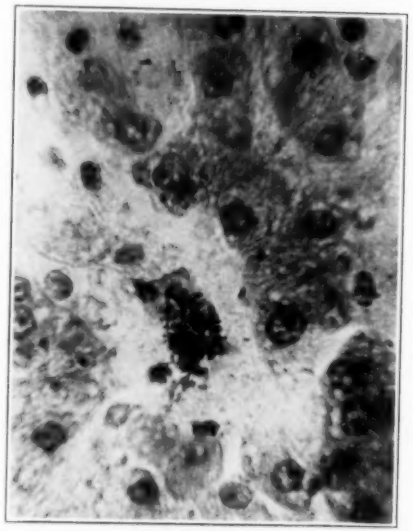

FIG. 5.—Case II. Liver, Gram-Weigert stain, high magnification. Degenerated and necrotic liver cells. Scattered cocci, and a large cluster in a group of necrotic liver cells.

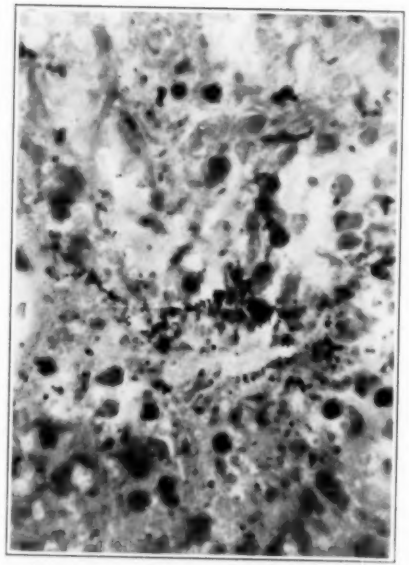

FIG. 6.—Case II. Spleen, Gram-Weigert stain, high magnification. Splenic cells mostly degenerated or necrotic; engorgement of blood spaces; numerous cocci.

FIG. 7.—Case I. Liver, Gram-Weigert stain, high magnification. Degeneration and necrosis of liver cells; numerous scattered cocci.

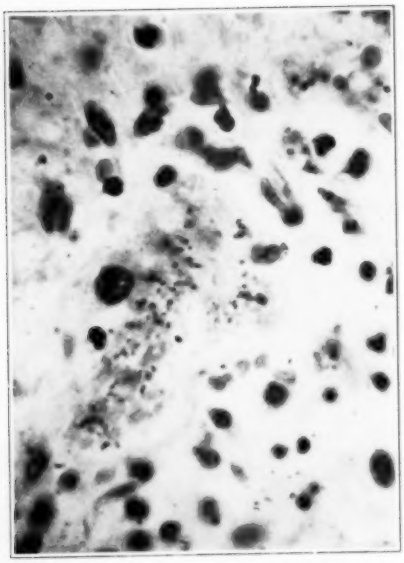

FIG. 8.—Case I. Spleen, Gram-Weigert stain, high magnification. Degeneration of splenic cells, fibrosis, engorgement, numerous cocci.

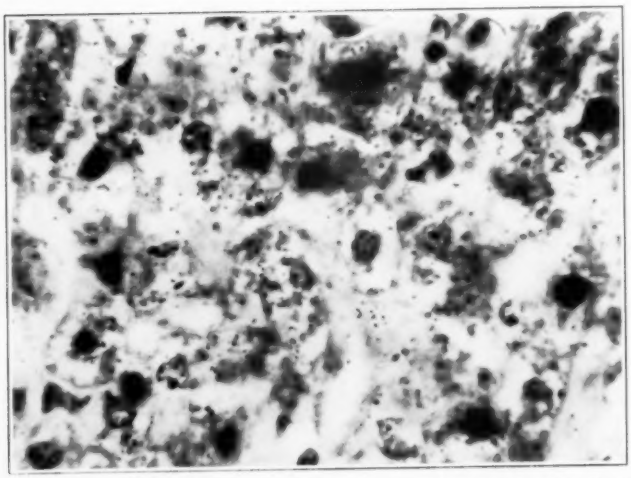

FIG. 9.—Liver of rabbit, killed seven days after a subcutaneous inoculation with hemolytic streptococcus, mixed with soft agar. This specimen was in fixative within five minutes after the rabbit was killed. Gram-Weigert stain, high magnification. Destruction of liver cells, congestion, numerous cocci.

Baginsky[4] cultivated a streptococcus from the heart blood and from substance obtained by puncture of a cirrhotic liver in 1 case.

Folger,[8] in 1 case, found streptococci in the liver; no cultures were made.

Weaver[16] produced cirrhosis in guinea pigs by injecting Bacillus coli into the portal circulation. Hektoen[9] reported similar experiments.

Notwithstanding the accumulated evidence suggesting infection as a cause, a thorough bacteriologic study of cirrhosis has not been made. The instances are rare in which bacteriologic examinations of any kind are recorded in either clinical or postmortem reports. The author is attempting such a study, and the following results are of the nature of a preliminary report:

**Case Reports.** Case I.—The patient, a girl aged twelve years, had no significant history except the indefinite mention of childhood diseases. Her symptoms were weakness, nosebleed and vomiting of blood. The skin was icteric, and the spleen greatly enlarged. Blood examination showed hemoglobin, 35 per cent; red cells, 3,500,000; white cells, 18,000, of which 60 per cent were polymorphonuclear and 40 per cent lymphocytes. Death occurred twenty-four hours following admission. The provisional diagnosis was Banti's disease.

Postmortem examination (Dr. B. L. Crawford) showed a spleen which was rough and fibrous and had irregular thickening of the capsule. The follicles could not be seen. The spleen weighed 930 gm. (Fig. 1). The liver was pale, shrunken, irregular, hard and nodular. Bands of fibrous tissue surrounded islands of liver cells. It weighed 980 gm. There was no ascites. Chronic hyperplasia of the spleen and chronic atrophic cirrhosis were the chief gross pathologic conditions.

On microscopic examination, the liver presented the usual picture characteristic of atrophic cirrhosis. The spleen was fibrotic; the pulp and follicles showed a decrease in cellular elements.

Sections of liver and spleen were stained by the Gram-Weigert (Figs. 7 and 8) method for demonstrating bacteria. Both the liver and spleen contained large numbers of cocci occurring in pairs, short chains and irregular groups.

The postmortem examination had been done too long before for cultures to be of value.

Case II.—A white boy, Joseph S., aged fourteen years, was rather small for his age. He was one of a family of 14, 8 of whom were living. One sister died of atrophic cirrhosis at the age of thirteen years with clinical features similar to those presented in this case. Some weeks subsequent to Joseph's death his brother, aged twelve years, was brought to the hospital with a greatly enlarged abdomen and essentially the same clinical features as Joseph had shown. His parents removed him from the hospital before clinical studies were completed. Joseph had had diphtheria but the parents gave no account of other infection. The younger brother was stated to have had scarlatina. The use of alcohol was denied both by the boy and the parents.

The condition began insidiously with no pain nor distinct malaise. Lassitude and swelling of the abdomen were first noted. Examination showed a greatly distended abdomen. The liver and spleen were greatly enlarged. No ascites was present on admission but developed in large quantities later. The hemoglobin was 47 per cent, the red cells 2,700,000 and the leukocytes

2600. There was no history nor evidence of syphilis. Blood Wassermann test was negative for each of the parents. The patient's blood was anticomplementary. The temperature ranged from 97.6° to 100° F.; on one occasion it rose to 102.4° F. The urine was concentrated and dark in color. Otherwise no abnormal urinary findings were noted. Slight icterus developed shortly before death. There was a slight tendency to bleed from insignificant injuries but no spontaneous hemorrhages. The course was progressive, ending in death ten weeks after the abdominal swelling first developed. No clinical diagnosis was made.

Postmortem examination (Dr. B. L. Crawford) showed slight icterus of the skin, prominence of superficial veins, distended abdomen and edema of the scrotum and legs. There was an excess of clear fluid in the pericardial, pleural and peritoneal cavities. The lungs were congested and showed early bronchopneumonia. The lymph nodes near the hilus of the liver and pancreas were about 2 cm. in diameter. They were soft and had a grayish-red color. The kidneys were slightly swollen and were pale.

The spleen weighed 1120 gm. It was smooth, firm and deep red, slightly mottled. It did not bleed when cut. Microscopically there was almost total absence of cells in the splenic pulp and of lymphocytes in the follicles. There was slight proliferation of fibrous tissue. The splenic sinuses were distended with blood and there was widespread recent necrosis of the cells of the splenic pulp.

The liver weighed 1330 gm. It was uniformly enlarged, pale yellow in color and the surfaces were roughened and nodular giving it a typical "hob-nailed" appearance. The nodules varied from 2 mm. to 1 cm. in diameter. The liver was hard and cut with marked resistance. The cut surfaces showed a marked proliferation of connective tissue surrounding small yellowish nodules of liver substance. Microscopic examination showed a marked cirrhosis, which differed from atrophic cirrhosis as seen in adults, only in that the process seemed more recent and more active than that usually seen in adult cases. Three processes marked the condition: Degeneration, necrosis and disintegration of liver cells; proliferation of liver cells and of bile ducts; abundant widespread proliferation of fibrous tissue, perilobular in distribution, but invading the lobules, where necrosis of liver cells was most marked. There was a moderate cellular infiltration, consisting mostly of lymphoid cells together with a small percentage of polymorphonuclear cells. These features strongly suggest a chronic infectious process, in which the inflammatory reaction shows proliferative rather than exudative features.

This case presented suitable opportunity for bacteriologic study postmortem. A small bit of liver was excised aseptically. Scrapings from it were streaked on blood agar, suspended in columns of melted agar and planted in broth. After twenty-four hours' incubation, there were hundreds of minute, grayish colonies on the blood-agar plates. Each colony was surrounded by a wide zone of hemolysis. No other type of colony was present. The columns of agar contained very numberous, small, grayish colonies throughout. The broth cultures were uniformly slightly turbid. Microscopic examination of each of these showed streptococci in perfectly pure culture. No other organism grew in any of the cultures.

Paraffin sections of the liver, stained by Gram-Weigert's (Fig. 5) method, showed numbers of cocci occurring in pairs, short chains and irregular clumps. The liver cells containing these cocci showed

advanced degeneration, many were necrotic and were undergoing disintegration. This condition was found diffusely throughout all parts of the liver. Sections of the spleen, stained by Gram-Weigert's (Fig. 6) method, showed likewise great numbers of streptococci, the distribution of which was not so diffuse, but rather tended to localization in small clumps. No bacilli nor other organisms were found in these sections.

It seems improbable that the streptococci found in the liver and spleen were the result of postmortem contamination for the following reasons:

Their presence in numbers was accompanied by necrosis of liver cells and more active cellular response than where the cocci were not so numerous. This would indicate their presence during life.

The streptococci were cultivated in pure culture and in large numbers. A postmortem invasion of the liver would probably have consisted of motile bacilli from the bowel tract. Such organisms appear earliest as postmortem contaminants.

The streptococci were found equally numerous in sections from the upper surface of the right lobe, the central portion and the portion adjacent to the colon. Postmortem spread of organisms would be most numerous adjacent to the bowels.

No organisms were found in sections of the kidney cortex, although sections taken from the anterior surfaces were examined. A postmortem spread of bacteria should involve the anterior portions of the kidney, at least as early as it would the entire substance of the liver and spleen.

Cultures of the heart's blood taken at autopsy remained sterile. This would be unlikely if either postmortem contamination or terminal septicemia were the occasion for the widespread distribution of streptococci in the liver and spleen.

Rabbits were inoculated immediately with the hemolytic streptococcus cultivated from the liver. Some received intraperitoneal injections of the centrifugalized sediment from broth cultures; others received similar sediment intravenously. In others, sediment containing streptococci was mixed with melted agar and injected subcutaneously. The latter method was designed to produce a slower absorption of the bacteria into the animal's circulation. It was an attempt to produce a chronic focus of infection from which invasion of the system might take place continuously.

The histories of the first four are given in detail. The remaining eight had exactly similar features following the inoculation except that in three there was an intercurrent infection of rabbit pneumonia, which was a factor in causing the death.

**Rabbit No. 1,** received 2 cc. of broth, very rich in bacteria, intraperitoneally. He became sick, ate very little, lost flesh and died four days after the inoculation. Postmortem examination was made within thirty minutes of death. The muscular tissues were pale; the liver much enlarged and very

dark red, the gall bladder greatly distended. The kidneys, spleen, adrenals, heart, lungs and joints appeared normal. Tissue or fluid from each of these areas was cultured. A pure culture of hemolytic streptococcus was obtained from the heart's blood and from the spleen and liver. Cultures made from the kidney, bile, muscle, joint fluid and peritoneal washings remained sterile.

**Rabbit No. 2,** inoculated subcutaneously with streptococci in agar, developed redness and swelling at the site of inoculation. Two days later he seemed slightly sick, slightly inactive, but continued to eat normally. Five days after inoculation he was again apparently normal and remained so until the eighth day when he was killed and examined. There was a localized abscess 1 cm. in diameter, at the site of inoculation. The liver was very large and dark red. The other organs and tissues appeared normal. Cultures were made as in rabbit No. 1. The streptococcus was recovered from the liver and from the subcutaneous abscess. It was not present in the cultures from the other sites. (See Fig. 9 for condition of liver.)

**Rabbit No. 3,** inoculated by subcutaneous injection of agar behaved similar to rabbit No. 2 and was apparently normal six days after the inoculation. He died and was examined ten days after inoculation. There was a subcutaneous abscess about 1.5 cm. in diameter at the site of the agar injection. The liver was dark red but not enlarged. The pericardium was distended with about 5 cc. of clear fluid. The peritoneum contained about 15 cc. of clear fluid. Cultures were made as before. The streptococcus was recovered in pure culture from the liver, the pericardial fluid and from the site of the agar injection. It did not appear in cultures from other sites.

**Rabbit No. 4,** was injected intraperitoneally with about 4 cc. of the original broth culture from the boy's liver. He was distinctly sick for several days but gradually recovered. Seven days later he was apparently normal except for lameness in the left leg, the knee joint of which was swollen and tender. Two weeks after inoculation he was killed and examined. The peritoneum showed no evidence of inflammation. The liver was very large and dark red. A local abscess was present in the mediastinum and the left knee was swollen and contained purulent material. All other structures appeared normal. Streptococci were recovered from the liver, mediastinal abscess and joint. Cultures from other sources including the peritoneum showed no growth.

The details and results of the experiment on rabbits are given in tabular form for the sake of brevity.

It will be seen from an inspection of the tabulated results from this group of rabbits that in 11 of the 12 animals the inoculated organism was recovered from the liver. The rabbit, No. S5, died at night and examination was made a number of hours later. Postmortem contamination of the organs in this rabbit made it impossible to determine accurately the presence or absence of the inoculated organism. Infection of the liver in these rabbits occurred regardless of the route or site of the inoculation. It was found also in the spleen in 5 of the rabbits. This may be significant in view of the fact that juvenile cirrhosis appears to be a splenohepatic disease rather than purely hepatic. Streptococci were demonstrated microscopically in the spleens of the human cases studied.

The fact that generalized infection and death did not occur regularly even when large numbers of streptococci were injected intravenously, indicates that the virulence of this particular strain

was low. Such a strain is well adapted to produce chronic infections. None of the rabbits in this experiment were allowed to live long enough for cirrhotic changes to occur. Experiments are being continued under conditions suitable to determine the effects of chronic infections with this streptococcus. Such results as may be obtained will be the subject of a later report.

RESULTS OF ANIMAL INOCULATIONS.

| Rabbit. | Inoculation. | Termination. | Days. | Streptococcus recovered by culture from: | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Liver. | Spleen. | Kidneys. | Blood. | Peritoneum. | Other sites. |
| S 1 | Peritoneal | Streptococcus infection | 3 | + | + | − | + | − | − |
| S 2 | Agar, subcutaneous | Killed | 6 | + | − | − | − | − | Subcutaneous abscess. |
| S 3 | Agar, subcutaneous | Streptococcus infection | 10 | + | − | − | − | − | Pericardium. |
| S 4 | Peritoneal | Killed | 13 | + | − | − | − | − | Mediastinal abscesses, joint. |
| S 5 | Peritoneal | Epidemic pneumonia | 20 | ± | ± | ± | ± | ± | ± |
| S 6 | Peritoneal | Streptococcus infection | 2 | + | + | − | − | + | − |
| S 7 | Intravenous | Epidemic pneumonia | 15 | + | − | − | − | − | − |
| S 8 | Intravenous | Epidemic pneumonia | 10 | + | − | − | − | − | Pericardium. |
| S 9 | Intravenous | Streptococcus infection | 5 | + | + | − | + | − | Gall bladder. |
| S10 | Intravenous | Killed | 6 | + | + | + | + | − | − |
| S11 | Intravenous | Killed | 6 | + | − | − | − | − | − |
| S12 | Agar, peritoneal | Streptococcus infection | 4 | + | + | − | − | + | Mediastinum; lung; pericardium. |

EXPLANATION: Under the termination "killed" the rabbit was always first anesthetized. The symbols + and − indicate the presence or absence of the organism in cultures from the organ. The symbol ± indicates indeterminate result.

Sections from livers of the rabbits showed extreme degeneration and destruction of liver cells. In many cases the cells were far advanced toward dissolution and no cells of normal appearance were to be found. Sections stained by Gram-Weigert's method showed very numerous cocci (Fig. 9). In some, these were diffusely distributed throughout the sections; in others there was some tendency to localization.

A remarkable feature was the deficiency of inflammatory response to the infection. Leukocytes were absent, or very few were present, even in areas where injury to the liver cells was extreme and where many cocci could be seen.

**Conclusions.**—Evidence from collected cases indicates that juvenile cirrhosis is a combined disease of liver and spleen.

The presence of streptococci in the liver and spleen was determined in 2 cases of atrophic cirrhosis occurring in children of school age.

The streptococci cultivated from the liver of one case showed a definite tendency to infect the liver in animals.

The histologic changes present in cirrhotic livers are such as would result from a diffuse infection of long duration.

Chronic infection of the liver should be regarded among the important causes of cirrhosis.

NOTE.—The author acknowledges indebtedness to the Medical Staff of Jefferson Hospital and to Dr. Crawford, pathologist, for their hearty coöperation in this study.

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## SCLEROSING TREATMENT OF VARICOSE VEINS BY CHEMICAL IRRITANTS.*

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THIS common, distressing, unaristocratic malady has been successfully treated by the intravascular injection of sclerosing solutions, in Europe since 1911. Pravatz[1] and others from 1851 to 1853 tried the injections of blood coagulating solutions such as perchlorid

* Read before the Hennepin County Medical Society April 15, 1928.

of iron, alcohol, tincture of iodin and Pregel's (isotonic iodin) solution. The severe reactions, infections and fatalities soon discouraged the pioneers in this field. In 1894, DeLore[2] showed that success was due to the reaction in the vein wall and not due to the coagulation of the blood. Then noncoagulating or anticoagulating solutions were tried with more success. The variety of the agents used testifies to the dissatisfaction experienced with first one and then another sclerosing agent. Not one of the agents met the ideal requirements, namely, certain action without unpleasant necessary symptoms. The agents used include mercuric chlorid, mercuric diiodid, sodium chlorid, argochrom, pyoktannin, quinin urethrane, sodium bicarbonate, sodium salicylate, and the like. In 1927, Kausch[3] introduced the use of invert sugar, which possesses most of the advantages with but few of the disadvantages of other sclerosing agents. Professor Nobl in some 10,000 injections in some 3400 cases, without a fatality, has proven the worth of invert sugar in the production of phlebosclerosis.

The varices herein considered are the enlarged tortuous external veins of the lower extremity. The cause most generally accepted is a combination of a hereditary or constitutional predisposition with the exciting cause, such as hydrostatic pressure from prolonged standing, heavy lifting, or any condition as abdominal tumor or pregnancy that will cause increased intraäbdominal pressure. Hallion believes the fundamental cause to be valvular deficiency in the upper portions of the vein. The experiments of Trendelenburg and Perthe, and as verified by Magnus[4] and Jentzer, have shown that there is a flow of blood in the peripheral direction when varices are present. This retrograde flow explains the paucity of emboli and the rapid formation of ulcers. The blood normally flows to the heart because of pressure of blood flowing from the capillaries. The deep veins suffice for the removal of blood from the tissues. Loss of function in the varicosed veins results in dilatations, engorgement, trophic skin disorders (such as ulcers and eczema), thrombophlebitis and hemorrhage; and gives rise to the symptoms of debility, fatigue, pain and leg cramps; and causes an unsightly appearance. Successful treatment results in the permanent obliteration and complete disappearance of the enlarged veins, and within a short time in an improvement of the previously disturbed circulation. Patients regularly report that the heaviness and fatigue disappear and they feel more efficient.

The delayed acceptance of this method of treatment by the medical profession has been due to the fear of emboli. A knowledge of the process of sclerosis should dispel this fear because the danger is chiefly theoretical. Animal experiments by Doerffel,[5] Regard[6] and Bazelis,[7] verified by Binet and Verne, have shown that an adherent clot is formed in veins injected with sclerosing agents. Their detailed macroscopic and microscopic studies of treated veins from

FIG. 1.—Mrs. A. O. No. 16748. July 1, 1927. (Before.)

FIG. 2.—No. 16748. April 1, 1928. (After.) Three injections Invertose; 3 injections sodium chlorid, 20 per cent.

FIG. 3.—Mrs. F. A. Y. No. 4226. November 8, 1927. (Before.)

FIG. 4.—No. 4226. January 25, 1928. (After.) Eight injections Invertose.

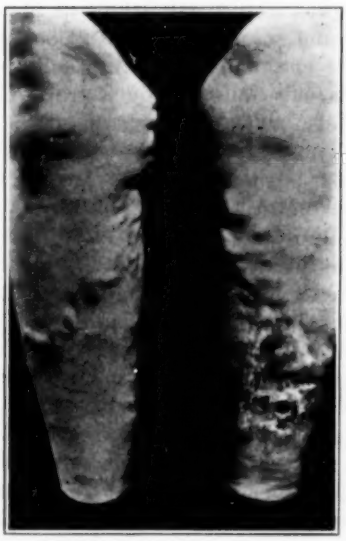

FIG. 5.—Mrs. S. No. 25263. June 23, 1927. (Before.)

FIG. 6.—No. 25263. October 12, 1927. (After.) Seven injections Invertose.

FIG. 7.—Mrs. C. No. 25036. May 11, 1927. (Before.)

FIG. 8.—No. 25036. October 11, 1927. (After.) Nine injections Invertose; 1 injection 20 per cent sodium chlorid. Note scar of slough after injections of sodium chlorid.

one to fifteen days after injection are well worth study in detail. Briefly, they show that the sclerosing solution acts as a chemical irritant to the intima, which results in a marked swelling and desquamation of endothelial cells, which is followed by a trabecular deposit of fibrin and blood platelets. Two factors are active in bringing about obliteration: (*a*) Unusually intensive proliferation of the intima building a trabecular structure in the lumen; (*b*) secondary formation of thrombi (excretory thrombus) induced by irritation of the intima, while in a purely mechanical fashion a stagnation thrombus forms in the meshes of the intima. Organization proceeds and progressive retraction takes place, resulting in a transformation of the vein into a thin fibrous strand, in which only a few muscle fibers are demonstrable. Meisen's[8] patient, who came to autopsy as a result of an accident while under treatment, showed the thrombus so adherent that it could not be expelled by pressure on the vein. The thrombus through its main extent had grown fast to the vein wall. Vessel offshoots showed adhesions with masses of connective tissue. Thrombus masses everywhere were fixed to the vascular wall by means of connective tissue. In view of these findings it is obvious why embolic phenomena have been rare.

While in Europe, one of us (R. C. L.) was so impressed with the good results from the use of invert sugar (calorose) that it was decided to use this form of treatment. Difficulty in obtaining the foreign product led to the preparation and use of a domestic product (invertose). All of the cases reported in this paper have been treated with this invert sugar solution. In some of the cases one or more veins have been treated with 20 per cent sodium chlorid solution for purposes of comparative study. We prefer the invert sugar because it is practically painless, nontoxic and sloughing does not occur following an accidental injection outside the vein. We have noted that the formation of thrombus proceeds more slowly but organization becomes complete. Canalization and recurrence is rare. The reaction in and about the vein (periphlebitis) is less likely to develop. This increases the factor of safety. We have noted no general reactions.

**Technique.** An effort is made to bring the sclerosing solution into contact with the intima in a maximum concentration. While the patient stands erect, the point of injection is selected and marked. The site should be as high up the vein as possible but never above the level of the lower third of the femur. In ulcer cases the practice is to first treat the veins apparently responsible for the ulcer. The patient then lies prone on the table and the skin about the site of the injection is sterilized as for any intravenous therapy. The blood is then gently "milked" from a section of the vein for a distance of a few centimeters above and below the site selected for injection. The assistant then applies firm pressure with the fingers at two points, one above and one below the site of injection, to keep the vein partly emp-

tied of blood. This firm pressure is maintained during the injection and for five minutes (by the clock) after the injection. A needle, 18- to 24-gauge, attached to a sterile glass syringe filled with the solution is carefully inserted into the vein at the site previously selected and marked. Blood is aspirated into the syringe to make certain the needle is well within the vein. The solution is then injected rapidly into the partly emptied vein until there is moderate distention. The amount required will vary from 5 to 20 cc., depending on the size of the varix. The moderate distention of the vein with the needle *in situ* is maintained for fully five minutes to properly affect the intima. A small thick gauze pressure dressing is applied over the treated area as the pressure is released and the needle withdrawn to prevent leakage from the vein. Adhesive strips are applied to maintain the pressure dressing for a period of two or three days. Where large, prominent, highly elevated veins have been treated, it is well to apply a pressure pad over the entire course of the vein, especially if the contraction phenomenon after injection has been noted. This pressure is maintained for a week or more until sclerosis is complete. The elastic bandage is applied from ankle to thigh. This hastens the disappearance of the vein. The patient is instructed to get up and go about as usual to attain best results.

**Summary of Cases Treated.** We wish to report our experience with 96 cases, 23 males, 73 females, average age forty-five years. The average number of injections necessary for each case was between 5 and 6. Ulcers were present in 20 cases, eczema in 8, and extensive edema in 8.

Some 63 injections of 20 per cent sodium chlorid solution were used in 28 patients. Sixty injections were followed by severe cramps, 4 patients fainted. In only 3 injections were the cramps slight. Ten of the injections were followed by periphlebitis. Failure to obtain sclerosis after the first injection of salt solution was noted several times. In one case no sclerosis was obtained after repeated injections of salt solution (as well as mercuric chlorid and invertose). Four injections were followed by tissue necrosis, three of the sloughs being attributed to accidental injection of the salt solution outside of the vein, and one from leakage through the needle puncture after injection.

Some 546 injections of invertose, 40 to 60 per cent, were made on 96 patients. Four of these were followed by severe cramps, 19 by moderate cramps, 231 by slight feeling of tightness, discomfort without actual pain and 292 without discomfort of any kind. Failure to obtain sclerosis after injection was noted in 17, and partial failure or slight sclerosis was noted after 56 injections, due to hyposensitive intima. Fifteen injections were followed by varying grades of periphlebitis. Although in several instances the accidental injection of 2 to 5 cc. of invertose outside of the vein was noted, but one slough followed, that in a case of a very old lady with unhealthy looking

skin. In this case, a small area of dry gangrene appeared along the course of the injected vein. In 4 cases, an extensive sclerosis was noted along almost the entire course of the internal saphenous magna, probably due to a hypersensitive intima.

The following complicating conditions were noted: Obesity in 12 cases, hypertension in 14 cases, diabetes in 2, nephritis 1, decompensated heart in 1, previously operated 7, and lues in 1 case; all of which were treated with good results. One case had extensive scars following burn of the legs, recurrences were noted after treatment. Two cases previous to treatment suffered from phlebitis. It was interesting to note that the areas of thrombosis which followed the phlebitis became recanalized while areas of veins obliterated by the sclerosing solutions remained closed. In 1 case of diabetes with eczema, Mrs. J., aged fifty years, we noted an exacerbation of the eczema after injections of invertose.

The results have been tabulated after six months observation: Unknown: 2 cases; fair in 2 cases; good in 92 cases; recurrence in 2 cases (incompletely treated).

**Complications.** Periphlebitis may be extensive and distressing. It differs definitely from the usual periphlebitis in that it is not due to an infection, there is no fever, the pain is not so continuous, and only the superficial treated vein is involved. It is usually caused by the injection of large amounts of strong solutions into closely adjacent veins. The treatment is rest and local applications of heat. Recovery is permanent and results are satisfactory.

Embolism is usually fatal. Few cases have been reported. Two cases, those of Meisen and Lomholt,[9] were admittedly due to large and hurried injections of 20 per cent sodium chlorid. One, that of Hammer,[10] followed an overdose of mercuric chlorid to a nephritic subject. Another, that of McPheeters,[11] died of pulmonary embolism two weeks after treatment with sodium chlorid, hence not definitely a result of treatment.

Accidental perivascular injection results in the development of slow healing slough with all concentrated strongly irritating solutions except invert sugar, where a painful somewhat indurated area obtains, and disappears in a few days or a week.

Nonsclerosis will disappoint the physician and the patient at times. Linser believes that it is always due to incorrect technique or insufficient strength of the solution, but an analysis of his cases show the occasional failure to obtain sclerosis even when using 40 per cent sodium chlorid. Cases of nonsclerosis have been recorded with all of the agents. We lean to the view of Revinovsky that individual idiosyncrasy is responsible for the occurrence of nonsclerosis. In some cases the intima seems unduly tolerant to the solution, or develops increased tolerance to the solution during the course of the treatment. Repeated injections in the same area every two days will usually bring about a sclerosis. Cases tolerant to one solution may be sensitive to other solutions.

Various men have reported the following contraindications to the use of this method of treatment: Cases of plethora with hypertension; cardiopathy, cardiorenal disease; pregnancy, large abdominal tumors; phleboliths, deep phlebitis, and recent superficial phlebitis.

**Conclusion.** We believe that the method of induced sclerosis is the method of choice in the majority of cases of varicose veins, and that invert sugar is the preferable agent for inducing the phlebosclerosis.

We believe this method of treatment is better than surgery for the following reasons: The danger of embolism is less; the cost to the patient is less; the amount of pain is less; there is no scar formation; recurrences are less frequent; and the patient is not confined to bed.

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## EXPERIMENTAL STUDY OF THE EFFECTS OF STIMULATION AND SECTION OF THE VAGAL INNERVATION TO THE BRONCHI AND THEIR POSSIBLE RELATION TO ASTHMA.*

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The chief characteristic of asthma is the recurrence of paroxysmal attacks of respiratory dyspnea which last a variable length of time, frequently until the action of some drug affords relief. The suddenness of the onset and the course of the attack suggest, as the under-

* Work done in Division of Experimental Surgery and Pathology, The Mayo Foundation. Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery, 1928.

lying mechanism, spasm of the bronchial musculature in response to some stimulus. It is fairly well established that the constrictor fibers to the bronchi travel by way of the vagi. It is also generally accepted that there are cases of reflex asthma. Accepting these two factors, and granting that bronchial spasm plays a large part in the production of the attack, one might assume that the stimuli that reach the lung and produce the asthmatic attack probably travel by way of the vagi.

The literature supports the theory of reflex asthma. Experimentally Carlson and Luckhardt showed contraction of the lung in the turtle resulting from rubbing of the posterior nares. Sluder reported a case in man in which an attack of asthma could be produced at will by the application of irritants to the sphenopalatine foramen. A great many cures of asthma have also been reported following correction of abnormal intranasal conditions. Abbott reported cases of ethmoiditis and asthma in which the asthma was relieved when the ethmoiditis improved and was made worse with the return of the ethmoiditis. Cases reported by Henderson and De Jong, in which cures of asthma followed operations for anal prolapse; chronic appendicitis, and pelvic abnormalities, suggest that asthma may be dependent on patholgic processes other than those in the nose.

Much benefit has resulted from the study of the hypersensitive cases of asthma in relation to anaphylaxis. Coca pointed out, however, a difference between atopic manifestations (asthma and hay fever) and anaphylaxis, but stated that both antibody and atopic reagin may exist stimultaneously. Much more remains to be learned about the way in which foreign-protein sensitization causes paroxysmal bronchial spasm. Two obvious mechanisms suggest themselves: one that the sensitized bronchiolar musculature, on coming in contact with antigen, fixes this very much like the sensitized uterine muscle fixes antigen *in vitro*,[6] and another that the bronchiolar spasm is essentially a reflex by way of the vagi, the sensory stimulus to this reflex being a local reaction in some part of the body, where generalized hypersentivity exists (so-called Arthus phenomenon).

The first hypothesis has been rather widely discussed in the literature, but the second has not been given the attention it seems to deserve. Cases of hay asthma, on the latter hypothesis, could quite possibly be the result of a vagal reflex, by way of the fifth nerve, ending in the eyes and nose. Sluder reported a case of asthma which would be difficult to explain except on a reflex basis. A patient who was sensitive to the pollen of ragweed suffered from an attack of severe asthma in midwinter when pollen was introduced into the sphenoidal sinus; the attack was stopped at once by the intrasphenoidal application of cocain.

This study was undertaken to determine whether a physiologic basis existed for a reflex mechanism in certain cases of asthma. An attempt was made to determine whether changes could be produced

in the lungs of experimental animals by various methods of stimulation of the vagi, similar to those found in lungs of asthmatic patients.

If certain cases of asthma are due to stimuli reaching the lung by way of the vagi, relief should result from a method of treatment

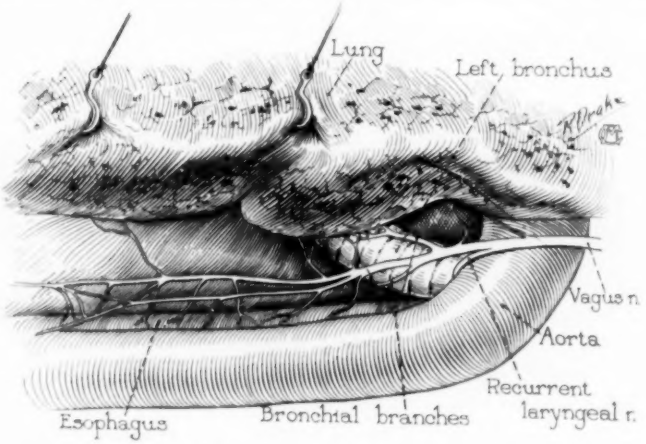


FIG. 1.—The course of the left vagus and its bronchial branches in the posterior mediastinum of man.

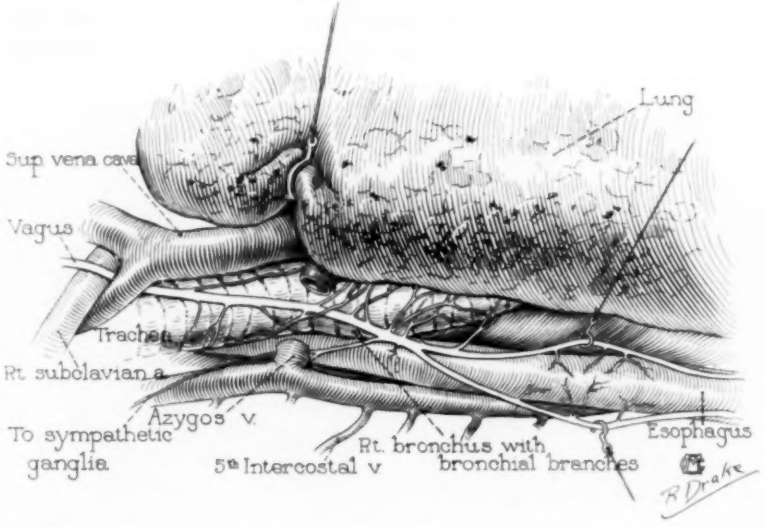


FIG. 2.—The course of the right vagus and its bronchial branches in the posterior mediastinum of man.

which would interrupt the pathway of these stimuli. Dissection of the bronchial branches of the vagi in the posterior mediastinum of a human being was therefore made (Figs. 1 and 2), and the effects of their section and evulsion studied in a series of dogs.

**Methods.** Guinea pigs, dogs and one monkey were used. For recording contraction of the bronchi following vagal stimulation in the dog, chloral hydrate anesthesia was induced, and both vagi were isolated in the neck. With the aid of a bronchoscope, a small rubber

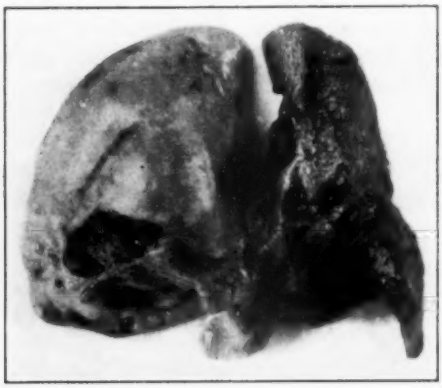

FIG. 3.—Lower lobes from the lungs of a guinea pig whose right vagus had been stimulated with resultant emphysema of the corresponding lung.

balloon, tied to a brass tube, was inserted snugly into a bronchiole of the left lower lobe. The opposite end of the tube was attached to a recording chloroform manometer. To obviate secondary

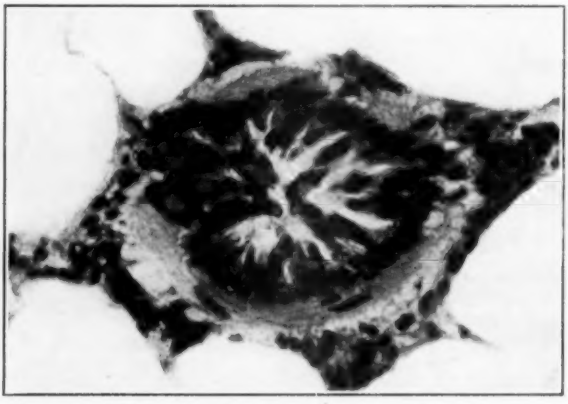

FIG. 4.—A bronchiole from the right lung of a guinea pig whose right vagus had been stimulated. The lumen is obliterated and there is apparent contracture of the musculature.

changes as a result of respiratory alterations following stimulation of the vagi, the thorax was opened. When respiratory activity had ceased the vagi were stimulated.

In the guinea pig, a special method was devised for demonstrating

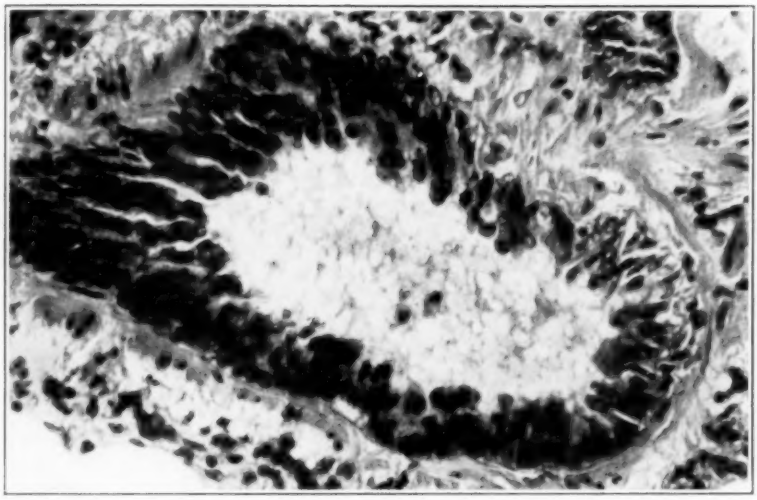

FIG. 5.—A large bronchiole from the lung of a guinea pig whose right vagus had been stimulated, showing more clearly the content of the bronchial lumen consisting chiefly of secretion.

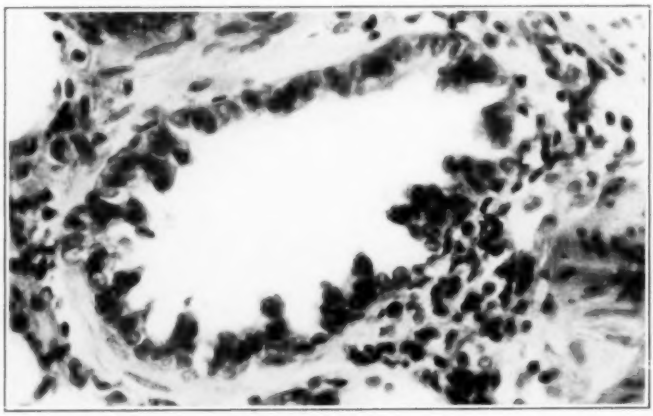

FIG. 6.—A bronchiole from the lung of a control animal treated in the same manner as the other animals except that the vagus was not stimulated. There is some irregularity in the epithelial outline and a small amount of content in the lumen.

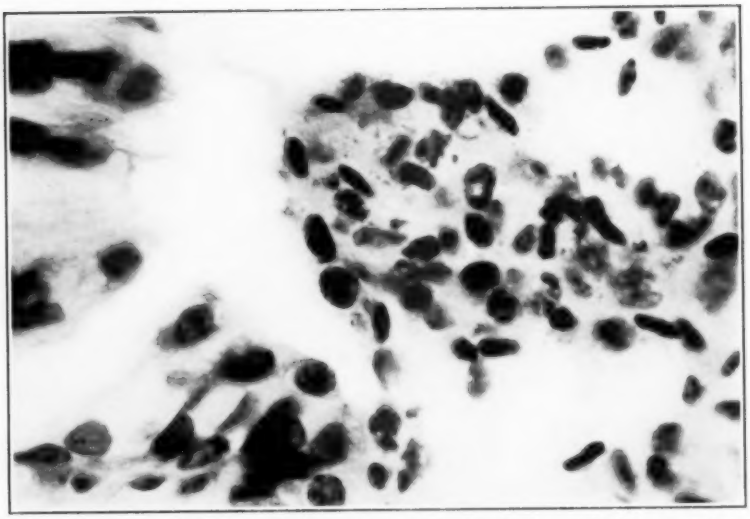

FIG. 7.—A bronchiole from the lung of a guinea pig whose vagi had been mechanically stimulated by sutures placed about them. The epithelium is stained poorly and shows definite changes with an irregular outline. There is an eosinophil in the bronchial lumen besides secretion and other cells.

bronchiolar spasm; this consisted essentially in immediate fixation of the animal in formalin after unilateral vagal stimulation under ether and later in comparison of the volume of the two lungs. In some guinea pigs the effects of simultaneous mechanical stimulation of the vagi were studied. For this purpose, tracheotomy was performed under ether anesthesia in order to rule out the possibility of dyspnea from paralysis of the muscles supplied by the recurrent laryngeal nerve. A ligature was placed under each vagus, and the skin infiltrated with procain and sutured. After the animal recovered from the anesthetic, and was breathing freely, and rhonchi were not audible with the stethoscope, the vagi were stimulated by gentle motion of the ligatures under them, and then the ligatures were tied loosely over the nerves so that they were not injured.

The guinea pigs in another series were sensitized to a fresh extract of horse dander by intraperitoneal injection of 1 cc. of a solution made up as described by Ratner, Jackson and Gruehl, and a method developed whereby dry dander could be blown into the nostrils.

In a study of the effects of section of the bronchial branches of the vagi, eight dogs were operated on under intratracheal ether insufflation anesthesia and strictly aseptic technique. The posterior mediastinum was reached by the transpleural route and the bronchial branches of the vagus were sectioned close to this nerve and evulsed. The nerves of one side only were sectioned at the first operation; on the other side they were sectioned two or three weeks later when the animal had recovered.

**Results.** Electrical stimulation of the peripheral end of the left vagus in the neck of a dog after section resulted in well-sustained contraction of the bronchioles of the left lung. Electrical stimulation of the right vagus gave bronchiole contraction in the left lung which was approximately half that resulting from stimulation of the left vagus.[11] These results were repeatedly obtained in the same animal.

Electrical stimulation of the peripheral end of the right vagus in the neck of the guinea pig often caused emphysema of the lung, giving this an appearance similar to that seen in anaphylaxis. The opposite lung appeared normal. The changes in the lung following stimulation of the vagus could be observed readily by opening the thoracic cavity during stimulation. In other experiments, when stimulation was commenced, the animal was killed by bleeding from the vessels of the neck. The whole animal was immediately fixed in 10 per cent formalin. The lung on the stimulated side was often definitely larger (Fig. 3); in one case its capacity was 10 cc. as compared with 5 cc. for the opposite lung. The experiments were controlled by repeating them on guinea pigs without electrical stimulation of the vagus. One must conclude, therefore, that electrical stimulation of the vagus in a guinea pig can cause pronounced emphysema of the corresponding lung, although the result

was obtained in only two thirds of the experiments. Failure was partly because of unavoidable trauma to the nerve incidental to the isolation for stimulation, and also, the method of electrical stimulation was found to be important.[14]

Microscopic study of the emphysematous lung revealed that the alveoli were distended and the lumen in many smaller bronchioles was entirely obliterated (Fig. 4). The epithelium stained poorly, and had lost its definite outline. The larger bronchioles were also partially or completely filled with secretion (Fig. 5), and there were peribronchial and parenchymal areas of cellular infiltration.

Although these microscopic changes did not occur in the control animals to any great extent (Fig. 6), it was considered advisable to repeat the experiments on pithed and decerebrate animals in which, following vagal stimulation, the lungs were immediately fixed either by excising a piece of lung and dropping it into formalin, or by the intravascular injection of fixing fluid. These experiments afforded data similar to those obtained when the vagi were stimulated.

Simultaneous mechanical stimulation of the vagi in the manner outlined caused dyspnea at once in all the experiments. Breathing was slow and labored, and rhonchi were easily heard with the stethoscope. These changes lasted from fifteen to sixty minutes, after which the animal appeared normal. The same response was produced on repeating the stimulation. Following these observations the animal was killed. In one animal of the series, which was killed while showing a well-marked reaction, the lungs were found to be emphysematous. In animals that had been dyspneic for an hour or more following mechanical stimulation of the vagi, the lungs showed secretion and cells in the bronchial lumen, including a few eosinophils (Fig. 7). In the parenchyma of the lung close to the bronchiole were typical eosinophils, and cells with typical eosinophilic granules but with an atypical nucleus.

On mechanical stimulation of one vagus, rhonchi were also produced in the corresponding lung in all instances which persisted and were similar to those occurring when both vagi were stimulated. The rhonchi were less persistent and fewer in number in the opposite side.

When the exposed vagi of a monkey were stimulated mechanically by a ligature, rhonchi resulted, with but little or no dyspnea.

On introduction of dry horse dander into the nostrils of guinea pigs previously sensitized to this material, a reaction occurred in 75 per cent of the animals tested. In the most outstanding result there was sneezing and rubbing of the nose, which, along with the eyes, dripped clear watery secretion. This was accompanied by severe respiratory dyspnea and the presence of rhonchi. The result was less marked although definite in other animals. It lasted a short but variable length of time, and could be repeated. In two hypersensitive animals tracheotomy was performed and the trachea tied off so that the dander could not come in contact with the mucosa of

the bronchial tree. After recovery from the anesthetic, the animal reacted to intranasal dander in a similar manner to the other animals.

Of the eight dogs operated on, one died from accidental pneumothorax. The remainder are well and apparently normal in every way three to four months after operation. These results are in harmony with those reported by Boothby and Shamoff, who studied the late effects of section of these nerves on gaseous metabolism, gas exchange and respiratory mechanism.

**Comment.** Although the literature related to this problem will not be discussed extensively, reference should be made to the very suggestive observations of Carlson and Luckhardt on lung reflex in turtles. As I have mentioned, these investigators found that rubbing of the posterior nares caused contraction of the lung, and Sluder reported a case in which an attack of asthma could be produced at will by the application of irritants to the sphenopalatine foramen.

The results reported following electrical and mechanical stimulation of the vagi in experimental animals are similar to those reported by Ellis in regard to the lungs of asthmatic subjects after death from severe attacks of bronchial asthma. It is possible that these experimental data may have a clinical bearing.

Unquestionably there are cases of reflex asthma of intranasal origin and cases are also reported in which cure has resulted from the correction of pathologic processes elsewhere in the body.

The group of cases now classified as chronic bronchitis with asthma may include cases of hypersensitiveness in which the protein is not known, and also cases in which there is a reflex origin outside the lungs. Chronic bronchitis may act as a point of irritation, causing reflex bronchial contraction of the musculature in the manner experimentally studied by Larsell and Burget.

Cases of asthma resulting from a reflex mechanism are best treated by elimination of the lesion at the point of irritation. If this fails, however, it might be worth while on the basis of these studies to section the bronchial branches of the vagi in the posterior mediastinum, using the extrapleural approach.

**Summary.** Physiologic and histologic observations were made on dogs, guinea pigs and one monkey with regard to the symptoms and changes produced by various types of stimulation of the vagi in the neck. In many cases the resultant changes in the lungs, bronchial constriction, bronchorrhea, cellular infiltration, and emphysema were similar to that seen in asthma. The studies thus establish a physiologic basis for the reflex nature of certain types of asthma.

The course of the fibers involved is presented and it was found that untoward symptoms did not result from their section in the dog. These experiments form the basis for the suggestion that in certain types of intractable asthma posterior mediastinotomy, with section of the bronchial branches of the vagi, using the extrapleural approach might be considered.

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## THE RELATIONSHIP BETWEEN SERUM CALCIUM AND AGE.

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**Introduction.** Our studies of plasma calcium in tuberculous adults[1] revealed similarity in calcium contents in the two sexes and suggested a tendency toward lower calcium contents with increasing age. We have investigated a large number of cases, in relatively

normal subjects, in order to gain further information regarding these points. Although statistical methods have been infrequently used in the treatment of data obtained in blood chemistry studies, we consider the time ripe for the use of such methods.

A review of the previous work on calcium will be given in chronological order. Loeper[2] believed that age influenced calcium content. Katzenellenbogen[3] studied the calcium content in infants on various diets. His results showed no constant relationship between the calcium in the diet and the content in the blood.

Lyman[4] in 54 cases found a lower calcium content in men than in women.

The results of the remaining investigations will be presented in tabular form.

| Investigators, cases | Age | Calcium, mg. | Remarks |
|---|---|---|---|
| Halverson and others.[5] | | | |
| Normal men | | 10.2 | 100 cc. serum |
| Jansen[6]. | | | |
| 7 | 7 wks–16 yrs. | 13.50–20.70 (CaO) | 100 cc. whole blood. |
| 4 men, 5 women | 20–30 yrs. | 12.46 | |
| 7 men, 4 women | 30–40 yrs. | 12.24 | |
| 3 men | 40–50 yrs. | 10.90 | |
| 2 women | 40–50 yrs. | 11.60 | |
| 4 men | Over 50 yrs. | 11.05 | |
| 4 women | Over 50 yrs. | 10.85 | |
| Howland and Marriott.[7] | | | |
| Infants | | 11.00 | 100 cc. serum. |
| Adults | | 9.20–11.30 | |
| Kehrer[8] | | 7.02– 7.53 | 100 cc. whole blood. |
| Talbott[9] | | | |
| 119 children | | 1.00–13.50 | |
| 22 adults | | 7.20–12.10 | |
| Jones and Nye.[10] | | | |
| 34 children | 4 wks.–14 yrs. | 10.00 | 100 cc. plasma. |
| Jones.[11] | | | |
| 22 infants | 4 hrs.–12 days | 12.30 | |
| Kramer *et al.*[12] | | | |
| Children | | 10.00–11.00 | 100 cc. serum. |
| Adults | | 9.00–10.50 | |
| Mayer.[13] | | | |
| Normal infants | | 11.25 (average) | 100 cc. serum, constant from week to week, on change with meals. |
| 7 | 4–10 yrs. | 11.38 | |
| De Wesselow[14] | | | |
| 17 nonpregnant women | | 9.90 | 100 cc. serum. |
| Leicher.[15] | | | |
| 60 normal | 1–20 yrs. | 11.60 | 100 cc. serum. |
| | 20–30 yrs. | 11.50 | |
| | 31–35 yrs. | 11.45 | |
| | 36–45 yrs. | 11.40 | |
| | 46–50 yrs. | 11.10 | |
| | Over 50 yrs. | 10.80 | |

| Investigators, cases. | Age. | Calcium, mg. | Remarks. |
|---|---|---|---|
| Herzfeld.[16] | | | |
| 70 | ..... | 11.00 | No variation with age. |
| Verified by Billigheimer.[17] | | | |
| Hess.[20] | | | |
| Infants with mild rickets | ..... | 7.50–13.00 | 100 cc. plasma. |
| Koechig.[21] | | | |
| 11 normal | ..... | 10.30 | |
| Jansen.[22] | | | |
| 120 pathologic cases | ..... | ... | Normal in most infections, but in croupous pneumonia 8.6–9.3 (CaO). |
| Tschimber.[24] | | | |
| Normal | ..... | 9.30–10.00 | |
| Anderson.[26] | | | |
| 40 children | 2 mo–11 yrs. | 10.70 | |
| Matz.[28] | | | |
| Normal | 16–43 yrs. | 10.28 | |
| Andersen.[29] | | | |
| 38 normal | Under 45 yrs. | 10.70 | |
| | Over 45 yrs. | 10.40 | |
| Wills.[31] | | | |
| 12 children | 2– 4 yrs. | 10.40 | |
| Di Foutsin[33] | 18–51 yrs. | 11.70 | |
| Nohlen.[34] | | | |
| 19 cases: Newborn | ..... | 12.65 | |
| Mothers | ..... | 11.40 | |
| Wyss.[35] | | | |
| Men | | 12.00–16.50 | No change with age. |
| Women | | 11.00–12.60 | |
| Rosen and Krasnow.[36] | | | |
| 50 medical students | | 11.60 | |
| Armstrong and Hood.[37] | | | |
| 101 neurologic patients | | 9.00–10.75 | |

The calcium content during pregnancy is still an unsettled question. Various authors have contributed information, but there is much disagreement among them (18, 19, 22, 25, 27, 30, 38 and 39). It is hoped that future work may help to solve this question.

Several methods of determining calcium have been used, such as the Wright, Lyman, de Waard, Tisdall and Kirth methods. The variations in results of different investigators may be attributed to slight differences in methods used. In spite of the great mass of work done, our questions were not answered satisfactorily by previous studies.

**Results.** These investigations were carried out on individuals as nearly normal as could be conveniently found at the various ages. The 7 to 17-year group was composed of children attending Lymanhurst School. These children were undernourished, but able to attend school regularly. Their homes were rather humble. Previous contact with open cases of tuberculosis and undernutrition made it advisable for them to be under constant observation at Lymanhurst.

The 18 to 28-year group was composed of students attending the University of Minnesota. Most of them were in excellent physical condition. The 29 to 39-year group contained several medical students, several members of the teaching staff, and some patients from the University Dispensary. The last came from such clinics as neurology, dermatology and internal medicine. All were up and about, and engaged in work.

The 40 to 50-year group included some attending physicians, and dispensary patients comparable to the previous group. The 51 to 61-year group contained some dispensary patients and some individuals who resided at Parkview Sanatorium. The latter were chronic cases, having such handicaps as decompensated hearts, arthritis and partial paralysis, but no acute infections. They were no longer able to work. The 62 to 72-year group included Parkview patients and dispensary patients, mostly from the ear and heart clinics. All above 72 years were of the same type.

The blood was drawn by venepuncture, about two hours after the last meal, in most cases. The blood was allowed to clot spontaneously and then centrifuged. Serum was used for the calcium determinations. Clark's[32] modification of the Kramer-Tisdall method was used. In almost every case duplicate determinations were made.

The results for women will be given first: 141 were studied, ranging in age from 7 to 83 years. The results for the different age groups are presented in Table I.

TABLE I.—RELATIVELY NORMAL WOMEN.

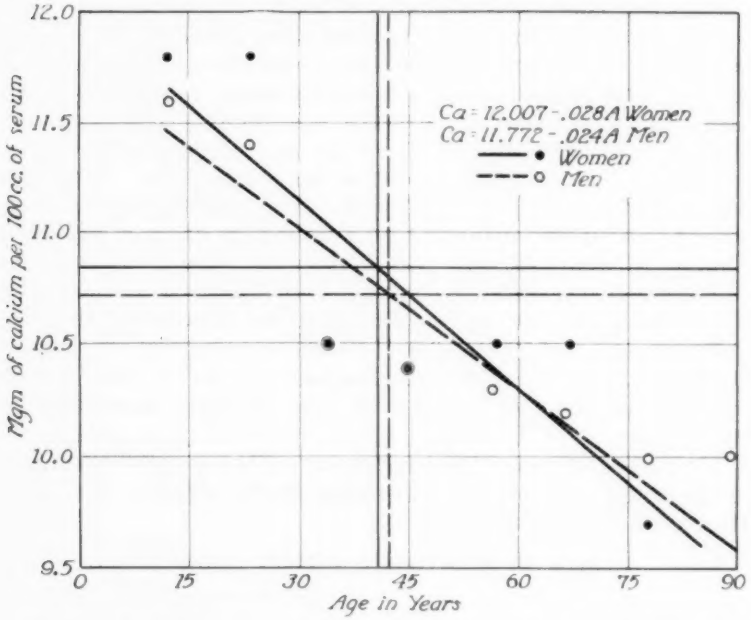
| Number of cases | Age group | Calcium in mg. per 100 cc. of serum. | | |
|---|---|---|---|---|
| | | Minimum. | Maximum. | Average. |
| 18 | 7–17 | 10.5 | 13.0 | 11.8 |
| 26 | 18–28 | 10.5 | 13.0 | 11.8 |
| 25 | 29–39 | 9.5 | 12.0 | 10.5 |
| 24 | 40–50 | 10.0 | 11.5 | 10.4 |
| 25 | 51–61 | 9.5 | 11.5 | 10.5 |
| 18 | 62–72 | 9.5 | 11.5 | 10.5 |
| 5 | 73–83 | 9.0 | 10.0 | 9.7 |

Examination of Table I reveals a decrease in calcium content with increasing age. The average age for all the women was $40.7 \pm 1.1$ years. The average calcium content for the entire group was $10.858 \pm 0.049$ mg.

The usual statistical methods have been employed. For advice in connection with the use of these methods we are greatly indebted to Prof. J. Arthur Harris. A study of the relationship between calcium and age gave a correlation coefficient, $r_{ACa}$ of $-0.617 \pm 0.035$ for the women. (A = age in years; Ca = milligrams of calcium per 100 cc. of serum.) The coefficient is 17.6 times as large as its probable error.

The linear regression equation, calculated from the means, standard deviations, and correlation coefficient is Ca = 12.007 −

0.028 A, where, as above, Ca = milligrams of calcium per 100 cc. of serum, and A = the age in years. The empirical mean calcium contents as ordinates are plotted against the age in the chart. The empirical means are distributed with some irregularity around the lines given by the equations, but without large numbers of cases further tests of linearity seem unnecessary.




The results for men are given in Table II. There were 177 cases, ranging in age from 7 to 94 years.

TABLE II.—RELATIVELY NORMAL MEN.

| Number of cases. | Age group. | Calcium in mg. per 100 cc. of serum. | | |
|---|---|---|---|---|
| | | Minimum. | Maximum. | Average. |
| 22 | 7–17 | 10.0 | 13.5 | 11.6 |
| 42 | 18–28 | 10.0 | 13.5 | 11.4 |
| 24 | 29–39 | 10.0 | 11.0 | 10.5 |
| 22 | 40–50 | 9.5 | 11.5 | 10.4 |
| 23 | 51–61 | 9.5 | 12.5 | 10.3 |
| 27 | 62–72 | 9.5 | 12.0 | 10.2 |
| 14 | 73–83 | 9.0 | 11.0 | 10.0 |
| 3 | 84–94 | 9.5 | 10.5 | 10.0 |

The calcium content decreases with age. The average age for all the men was $42.3 \pm 1.1$ years. The average calcium content for the entire group was $10.746 \pm 0.045$ mg. A study of the relationship between calcium and age gave a correlation coefficient, $r_{A\,Ca}$, of $-0.594 \pm 0.033$ for the men. The coefficient is 18 times as large as its probable error.

The linear regression equation is Ca = 11.772−0.024 A. The empirical mean calcium contents as ordinates are plotted against the age in the chart.

Comparison of the two sexes shows that the age difference is only 1.6±1.5 years, the average being 40.7±1.1 for the women and 42.3±1.1 years for the men. Thus the age groups are essentially comparable in years.

The difference in the average calcium content of men and women is 0.112±0.066 mg. Since the difference is only 1.7 as large as its probable error, it cannot be asserted to be significant.

The difference in correlation in men and women is 0.023±0.048. Thus the correlations for the two sexes are in excellent agreement. This lends strong support to the conclusion of the existence of a material negative relationship between age and the calcium content of the serum.

**Summary and Conclusions.** 1. The average calcium content of the serum was found to be 10.858±0.049 mg. in 141 women and 10.746±0.045 mg. in 177 men. Thus, while the calcium content of the serum of women is 0.112±0.066 mg. higher than that of men of comparable years, the difference may not be statistically significant.

2. The calcium content definitely decreases with age; in women it falls from an empirical average of 11.8 mg. at the age of 12 years to 9.7 mg. at the age of 78 years. In men it falls from 11.6 mg. at the age of 12 years to 10.0 mg. at the age of 78 years.

3. This decrease in calcium content can be quantitatively measured in terms of correlation. The correlation coefficient, $r_{\text{A Ca}}$, for women is −0.617±0.035; for men it is −0.594±0.033.

4. If we accept the graduation of the means given by the straight-line regression equation the calcium content falls from 11.727 mg. at 10 years to 9.767 mg. at 80 years in women, and from 11.532 mg. at 10 years to 9.852 mg. at 80 years in men.

5. On the basis of the present data we conclude that there is no statistically significant difference in the mean calcium content or in the intensity of correlation of calcium content with age, in the two sexes.

NOTE.—We desire to express our gratitude to Profs. J. Arthur Harris and Clarence M. Jackson for valuable criticism in the preparation of the manuscript.

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## MERCUROCHROME AS A BILIARY ANTISEPTIC, AS A MEANS TO VISUALIZE GALL BLADDERS, AND AS A POSSIBLE FORM OF TREATMENT IN CHOLECYSTITIS.

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On account of the previous work of Hill and Scott[1] on the hepatic excretion of mercurochrome in rabbits, we were stimulated to undertake the present study. They demonstrated that mercurochrome is excreted in large amounts by the liver and, furthermore, that the drug may be present in the bile in bactericidal quantities. They were also able to prove that artificially produced infections of the gall bladder could be controlled by the intravenous injection of the dye.

Studies have been made by others, some of which agree with the findings of Hill and Scott and some of which are contradictory.

Hench, Snell and Greene, in 1924,[2] working with dogs, found that mercurochrome is concentrated and excreted by the liver without significant changes in the liver function, as determined by phenoltetrachlorphthalein tests and by levulose tolerance tests. In a later paper,[3] these authors confirmed their previous work in dogs, but found that, in these animals, bile, after the intravenous administration of mercurochrome, did not have the bactericidal action anticipated from *in vitro* tests. These authors believed that the bactericidal power of the drug was reduced by some conjugation or alteration during its excretion. Simmons[4] found that mercurochrome (1 to 5000) in ox bile, killed typhoid bacilli in thirty minutes and (1 to 10,000) in one hour. The amount of culture and drug used in these tests was not given. However, he cites the work of Nichols, who failed to sterilize with intravenous injections of mercurochrome the bile of rabbits. These animals had previously received inoculations of 4 cc. of a heavy salt solution suspension of typhoid bacilli intravenously. He fails to consider that there is a possibility of other foci than the gall bladder. Simmons also cited Nichols' treatment of one human typhoid carrier with mercurochrome by mouth, for a week without benefit; a finding which we are able to confirm by further studies presented in this paper. Myer, Somer and Eddie[5] were unable to obtain sterilization of rabbits immunized with standard typhoid vaccine and inoculated intravenously or intracystically with Eberthella typhi; although they found that the hepatic bile of rabbits which had received intravenous mercurochrome could destroy 10,000,000 typhoid bacilli in from six to twenty four hours. Zeligs[6] has reported a case of acute typhoid cholecystitis in which the bile was sterilized by one intravenous injection of the drug; and Young,[7] in his series of case reports includes one of a patient with biliary fistula in which the bile, after intravenous mercurochrome, contained the dye.

**A. Oral Administration of Mercurochrome.** The work was started both upon what were thought to be definite cases free from gallbladder diseases and on cases about which there seemed to be no doubt as to the certainty of a cholecystitis. Seven of these cases had definite evidence of biliary disease. Four of them have subsequently been operated upon and a histopathologic diagnosis of cholecystitis has been made upon them. Three had stones. In 1 patient with arthritis a good result might possibly have been expected but was not obtained. In the other five it would be impossible to expect any therapeutic advantage from the dye.

(*a*) *Method.* Control duodenal drainages were done upon all cases prior to the administration of the dye. The position of the tube was fluoroscopically determined and the resultant flow was collected in a series of centrifuge tubes.

After thorough centrifugalization of a portion of the B bile which is supposedly from the gall bladder, 5 cc. of it was inoculated with a loopful of a virulent eighteen-hour broth culture of typhoid bacilli.

This was incubated twenty-four hours and two loopfuls were smeared upon Russel's agar. In all cases there was a luxuriant growth both of the typhoid bacilli and of contaminations present in the bile before inoculation.

The patients were then given salol coated tablets of mercurochrome varying from 200 to 500 mg. a day for a week. At the end of this time they were again drained and a repetition of the bacteriologic method listed above was carried out.

Chemical tests for the presence of mercury were also made on the successive specimens of bile.

(*b*) *Mercury Test.* 1. About 12 to 15 cc. of bile were mixed with an equal amount of concentrated hydrochloric acid and allowed to stand in the incubator overnight.

2. This was filtered into petri dishes and 5 to 7 small copper plates were scattered through the solution and allowed to stand overnight again at room temperature. (The copper plates had previously been thoroughly cleaned in concentrated nitric acid.)

3. The acid-bile mixture was decanted off the copper plates which were then thoroughly washed in tap water.

4. The plates were next heated over a Bunsen flame in a long pyrex test tube just comfortably wide enough to permit their insertion. Condensation was brought about by wrapping the portion of the tube near its mouth in wet filter paper or wet cloth. It was safest to heat until the plates were bronzed in appearance before they were dropped out.

5. A small crystal of iodin was dropped into the bottom of the tube after it had cooled off. If the iodin did not vaporize immediately gentle heat was applied.

When mercury was present the iodin united with it, with the formation of a brilliant red mercuric iodid just below that portion of the tube which was cooled during the original heating of the plates. The iodid usually appeared in long streaks. If large amounts of mercury were present a pretty web formation was seen.

As a control, we added 1 mg. of mercury in the form of mercurochrome to untreated bile. This gave a very definitely positive test.

(*c*) *Results of Oral Administration.* In 13 cases orally treated, we never saw a mercurochrome tint to the bile. Faint traces of mercury were found in 4 cases but never in sufficient concentration to have an inhibitory effect upon the growth of typhoid bacilli.

In this series of cases we were not able to see that the slightest improvement was obtained through this form of treatment.

So far as the routine urine tests might show there were no gross kidney changes. The van den Bergh reaction did not change one way or the other. As a matter of interest diastase tests[8] were run upon the B fraction of each drainage. No significant change was found in the strength after the week of mercurochrome treatment.

Most of the patients became salivated at some time during treatment and two of these had considerable trouble and distress.

TABLE I.—DUODENAL DRAINAGE BEFORE AND AFTER ORAL ADMINISTRATION OF MERCUROCHROME.

| Case. | Diagnosis. | Duodenal drainage before mercurochrome. | | | | | Duodenal drainage after oral administration of mercurochrome. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Diastase. | Types of bile. | As media for Typhosus B. | Urine albumen. | van den Bergh. | Diastase. | Types of bile. | As media for Typhosus B. | Urine albumen. | van den Bergh. | Mercury in 10 cc. bile. | Mg. mercury administered daily. | | Remarks. |
| 1 | Cholelithiasis | 63 | No "B" | Excellent | 0 | ½ U. indirect | 72 | No "B" | Excellent | 0 | ½ U. indirect | Trace | 400 for 10 days | Salivation | Same. |
| 2 | Cholelithiasis | 100 | Normal | Excellent | Trace | 0 | 88 | Normal | Excellent | Trace | 0 | 0 | 300 for 7 days | .. | Worse. |
| 3 | Cholelithiasis | 33 | Normal | Excellent | Trace | 1 U. indirect | 27 | Normal | Excellent | Trace | 1 U. direct | 0 | 500 for 5 days | Salivation | Same. |
| 4 | Cholecystitis | 50 | Light "B" | Excellent | Trace | 1½ U. indirect | 48 | Normal | Excellent | Trace | 1½ U. indirect | Trace | 400 for 7 days | .. | Same. |
| 5 | Chronic appendix | 53 | Normal | Excellent | 0 | 0 | 48 | Normal | Excellent | 0 | 0 | Trace | 200 for 7 days | Salivation | Same. |
| 6 | Neurosis | 42 | Normal | Excellent | 0 | 0 | 46 | Normal | Excellent | 0 | 0 | 0 | 400 for 7 days | Salivation | Much better. |
| 7 | Cholelithiasis | 86 | Normal | Excellent | Trace | 0 | 88 | Normal | Excellent | Trace | 0 | 0 | 400 for 7 days | .. | Same. |
| 8 | Schizophrenia | 46 | Light "B" | Excellent | 0 | 0 | 51 | Normal | Excellent | 0 | 0 | 0 | 400 for 7 days | .. | Same. |
| 9 | Cholecystitis | 92 | Normal | Excellent | Trace | 0 | 90 | Normal | Excellent | 0 | 0 | 0 | 600 for 7 days | Salivation | Same. |
| 10 | Cholecystitis | 40 | Normal | Excellent | 0 | 0 | 20 | Normal | Excellent | 0 | 0 | 0 | 400 for 7 days | Salivation | Worse. |
| 11 | Neurosis | 92 | Normal | Excellent | 0 | 0 | 102 | Normal | Excellent | 0 | 0 | 0 | 500 for 7 days | .. | Same. |

TABLE II.—SUMMARY OF EXPERIMENTS ON BILE AFTER INTRAVENOUS INJECTION OF MERCUROCHROME.

| Case. | Diagnosis. | Test No. | Treatment. M–220 (cc.). | Treatment. No. of specs. | Treatment. Notes. | Laboratory findings. Macroscopic appearance of bile. | Laboratory findings. Amount of mercury. | Bacteriologic findings. | Remarks. |
|---|---|---|---|---|---|---|---|---|---|
| 12 | No biliary disease | 1 | 20 | 8 | 3 cc. $MgSO_4$ between (3) and (4) | Stained in (4) 23 min. after injection of dye | +(5–8) | 1-hr. sterilization in (6); 24-hr. sterilization in (5–8). | |
| 14 | No biliary disease | 1 | 20 | 7 | 60 cc. $MgSO_4$ | Fluorescence throughout, "B" particularly stained | Trace in (7) | 24-hr. inhibition; 48-hr. sterilization in (7). | |
| 15 | Chronic biliary; U.R.Q. adhesions | 1 | 20 | 9 | 40 cc. $MgSO_4$ | Fluorescence | + to ++++ | 24-hr. sterilization in (5, 7); reduction to 2 colonies in (6). | Symptoms unchanged. |
| 16 | Chronic arthritis | 1 | 20 | 6 | .... | Fluorescence | 0 | Inhibition in (4–6) | Copper plates in HCl in 5 days. |
| 17 | Renal lithiasis | 1 | 20 | 6 | .... | Much fluorescence and dye in (1–3), less in (4–6); tube slipped, bile diluted | +++ in (1–3); + in (4–5) | 24-hr. sterilization in (2) and reduction to 6 colonies in (3). | |
| | | 2 | 20 | 6 | .... | ..... | 0 to +++ | 24-hr. sterilization in (5); colon bacillus persisting in the other tubes, no E. typhi. | |
| 18 | Chronic biliary disease | 1 | 20 | 8 | .... | Fluorescence, staining, decreased at the end | 0 to ++++ | 24-hr. sterilization | Much better. |
| | | 2 | 20 | ... | Drainage 24 hrs. after injection; not fasting | Very little dye | 0 | No inhibition | No symptoms 4 months after second injection. |
| 19 | Cholecystitis | 1 | 20 | 8 | .... | Very heavy dye | + to ++++ | 24-hr. sterilization | Much better. |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 2 | 20 | 8 | Drainage unsatisfactory; $MgSO_4$ before and after tube in duodenum | Very little dye | 0 | No inhibition | No symptoms 6 mos. after second injection. |
| | | | 3 | 20 | 7 | .... | ..... | .... | Inhibition in (1–3). | |
| 20 | . . . | Cholecystitis; cholelithiasis | 1 | 20 | 7 | .... | Very little dye | .... | No inhibition | No improvement. |
| | | | 2 | 20 | 6 | .... | Fairly heavy dye | + to ++ | 24-hr. sterilization of E. typhi in (1–3); staph. present before inoculation persisting | No improvement. |
| 21 | . . . | Cholecystitis | 1 | 12 | 9 | .... | Small amount of visible dye | Not done | No inhibition. | |
| 22 | . . . | Cholecystitis | 1 | 20 | 6 | .... | No dye or fluorescence | 0 | No inhibition | Much better. |
| | | | 2 | 20 | 5 | .... | ..... | ++ in (6) | Inhibition in (1). | |
| 23 | . . . | Cholecystitis | 1 | 20 | 7 | .... | Heavy stain (1–6) | .... | 24-hr. sterilization E. typhi in one specimen | Better? |
| 24 | . . . | Neurosis | 1 | 20 | 7 | .... | Heavy stain (1–5) | .... | 24-hr. sterilization E. typhi in one specimen | Much better. |
| 25 | . . . | Cholecystitis | 1 | 20 | 5 | .... | Heavy stain (3–5) | .... | 24-hr. reduction to 14 colonies in (5) and to 5 in (5). | |
| 26 | . . . | Chr. cholecystitis; appendicitis | 1 | 20 | 8 | Drainage 18 hrs. | Heavy (2–4), little (1, 8)—See Table III. | | | |
| 27 | . . . | Neurosis | 1 | 20 | 7 | | | | | |
| 28 | . . . | Neurosis | 1 | 12 | 5 | .... | ..... | .... | No inhibition. | |
| 29 | . . . | Neurosis | 1 | 20 | 6 | .... | ..... | .... | 24-hr. sterilization of E. typhi in (3). | |
| 32 | . . . | Cholecystitis | 1 | 12 | 5 | .... | ..... | ++ (2); + (4); +++ (3, 5) | Sterilization of E. typhi but not of coccus in (1–4). | |

**B. Intravenous Administration of Mercurochrome.** The determination of the hepatic excretion of dye after intravenous injection in man was next attempted.

(*a*) *Method.* 1. Intubation of patient with duodenal tube—position of bulb in duodenum was controlled by the fluoroscope as usual.

2. Intravenous injection of 20 cc. of 1-per cent mercurochrome.

3. Immediate stimulation of flow of bile by injection through the tube of 40 cc. of warmed 30-per cent magnesium sulphate.

4. Collection of resultant bile flow into sterile tubes. Capacity of tubes 20 cc.

5. Timing the appearance of first flow of bile and length of time through which it appeared.

6. Inoculation of bile specimens with typhoid bacilli or other organisms to determine germicidal or inhibitory qualities of mercurochromized bile. We used typhoid bacilli on account of their well known bilophilic qualities.

About 12 cc. of all the specimens were centrifugalized at a high speed for twenty to thirty minutes. One cubic centimeter from each tube was placed in a sterile Wassermann tube and inoculated with one large loopful of an eighteen-hour culture of typhoid bacilli. Immediately after the inoculation, 0.1 cc. of the organism-bile mixture was transferred to an agar slant to serve as a control for the number of organisms present at the beginning of the test. After twenty-four hours incubation at 37.5 C., another 0.1-cc. transfer was made in the same way, to determine the number of organisms left. In this way, it was possible to determine whether or not there had been sterilization or inhibition both of typhoid bacilli and of contaminations at times present in the bile before inoculation.

The bile remaining, after the withdrawal of the amounts desired for bacteriologic study, was mixed with equal amounts of concentrated hydrochloric acid and the test for mercury carried out as described above.

(*b*) *Immediate Effect of Intravenous Mercurochrome upon Bile.* Bile tinted with mercurochrome appeared in the siphoned bile between eighteen and twenty-three minutes after its intravenous injection. It continued to run in fairly high concentration for about fifty-five minutes. At the end of this time the tube was withdrawn. During the experiment, it was necessary to instil another 20 cc. of magnesium sulphate as the flow was becoming rather weak. Perhaps a third injection might have produced similar results.

About 15 to 20 cc. of the bile was collected into a series of tubes. Three of them were filled before the onset of the appearance of the dye and seven afterward. All were tested in the same manner for:

1. Bacterial qualities: The first three tubes showed no inhibition; tubes 4 to 10 showed varying amounts of inhibition to sterilization.

2. Chemical qualities: Tubes 1 to 3 showed no mercury; tubes 4 to 10 contained mercury in varying amounts.

FIG. 1.—Gall bladder. Duodenal tube in stomach.

FIG. 2.—Gall bladder. Duodenal tube in duodenum.

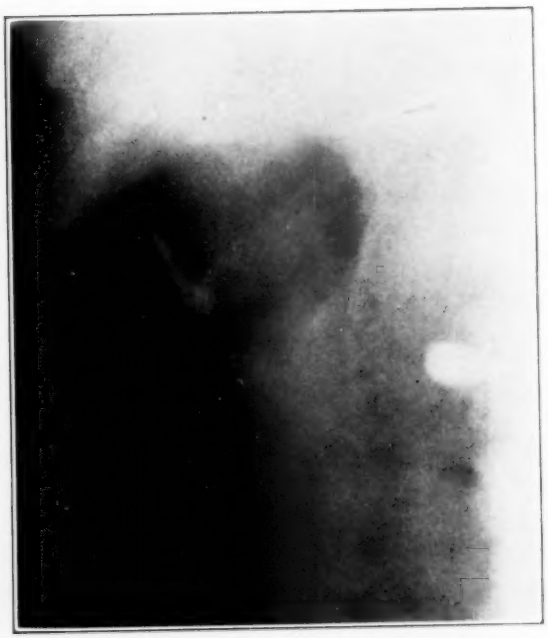

FIG. 3.—Gall bladder. Tube in pylorus.

(*c*) *Ability of the Gall Bladder to Store Mercurochromized Bile.* After the demonstration that bactericidal bile is excreted by the liver following the intravenous injection of mercurochrome, it became a matter of great interest to see if this type of bile could be stored in the gall bladder.

**Method.** Boyden[9] and Whitaker[10] have shown that the most complete emptying of the gall bladder may be obtained by the oral administration of egg yolk and cream. Consequently our patients were given the yolk of four eggs and a glass of half cream and half milk at noon. At 4.30 P.M. they were given varying amounts of mercurochrome by vein. Males usually received 20 cc. of a 1 per cent solution, females smaller amounts varying from 5 to 17 cc. After the milk-and-egg meal they fasted until the completion of the drainage. They reported to the dispensary the next morning when they were intubated with a duodenal tube (position controlled by fluoroscope). In the later experiments, it became routine to get Roentgen ray films of all the gall-bladder areas before and after the instillation of magnesium sulphate.

After siphonage was instituted, the bile was collected in a series of nonsterile centrifuge tubes; the contents of each tube was examined for its general appearance, that is, whether or not it contained visible amounts of the dye, its bactericidal qualities, and its mercury content. The tests described above were used for this purpose. Some of the more interesting findings will be recorded in detail.

**Laboratory Results.** A total of 25 complete examinations on 19 patients with 100 bile specimens have been collected and the end results are herein reported. Many other examinations have been attempted but for one reason or another have been incomplete. It has been of great interest to us to note the consistency with which siphoned bile contained considerable mercurochrome. At times the typical fluorescence was quite heavy. It was present in greatest concentration in the B bile which, as stated above, is supposed to come from the gall bladder itself and certain Roentgen ray evidence adds considerable weight to this theory.

In the 25 tests, a lack of inhibition was found only in 7 (28 per cent). In 4 tests (16 per cent) there was inhibition in some of the tubes. In 14 tests (56 per cent) there was sterilization; that is in 18 of the 25 tests (72 per cent) there was either sterilization or inhibition.

The mercury content has been measured by a qualitative method, but even so it is possible to gauge the amount into more or less rough groups which we have designated + to ++++. In the majority of cases the amount of mercury has been proportional to the bactericidal or inhibitory strength of the specimen. At times small amounts of mercury have been found without any inhibition to bacterial growth. This was also seen in the cases which were treated with mercurochrome by the oral route. There was no inhibition without the presence of mercury. Details of 2 cases are presented.

**Case Report.** CASE I (No. 32).—Colored female.
Dosage, 17 cc. mercurochrome at 4.30 P.M.
Drainage, 11.30 A.M. next day. Five tubes collected.
Bacteriologic and chemical method as described above.

(*a*) SUMMARY OF RESULTS.

| Tube. | Colonies before inoculation with Eberthella typhi. | Colonies 1 min. after inoculation with Eberthella typhi. | Colonies 24 hrs. after inoculation with Eberthella typhi. | Amount of mercury. |
|---|---|---|---|---|
| 1 | 15 of Gram coccus | Massive growth of E. typhi, scant coccus | No E. typhi, 100 of Gram coccus | + |
| 2 | 20 of Gram coccus | Massive growth of E. typhi, scant coccus | No E. typhi, 20 of Gram coccus | ++ |
| 3 | 20 of Gram coccus | Massive growth of E. typhi, scant coccus | No E. typhi, 10 of Gram coccus | +++ |
| 4 | 55 of Gram coccus | Massive growth of E. typhi, scant coccus | No E. typhi, 30 of Gram coccus | + |
| 5 | 20 of Gram coccus | Massive growth of E. typhi, scant coccus | Heavy growth of both organisms | +++ |

TABLE III.—BACTERICIDAL POWER OF DUODENAL FLUID FROM CASE II.

| Tube. | Time. | Plate. | Control uninoculated. | Eberthella typhi. | Eberthella dysenteriæ Flexner. | Streptococcus pyogenes. | Staphylococcus aureus 209. | Amount of mercury. |
|---|---|---|---|---|---|---|---|---|
| 1 | Start | A. | 100 G. + c. and b. | Over 200 | Infinite | Over 200 | Infinite | ++ |
| | 1 min. | B. | 100 G. + c. and b. | 65 | Over 200 | Over 200 | 100 | |
| | 24 hrs. | A. | Sterile | Sterile | Sterile | 100 | 1 | |
| 2 | Start | A. | 50 G. + c. and b. | Infinite | Infinite | Over 200 | Infinite | ++ |
| | 1 min. | B. | 50 G. + c. and b. | Over 200 | Over 200 | Over 200 | Over 200 | |
| | 24 hrs. | A. | Sterile | Sterile | Sterile | Slight reduc. | Over 200 | |
| 3 | Start | A. | Sterile | Infinite | Infinite | Over 200 | Infinite | +++ |
| | 1 min. | B. | .... | Over 200 | Over 200 | Over 200 | Over 200 | |
| | 24 hrs. | A. | .... | Sterile | Sterile | 1 | Over 200 | |
| 4 | Start | A. | Sterile | Infinite | Infinite | Over 200 | Infinite | + |
| | 1 min. | A. | .... | Over 200 | Over 200 | Over 200 | Over 200 | |
| | 24 hrs. | B. | .... | Over 200 | Over 200 | 4 | Slight reduc. | |
| 8 | Start | A. | Sterile | Infinite | Infinite | Over 200 | Infinite | + |
| | 1 min. | B. | .... | Over 200 | Over 200 | Over 200 | Over 200 | |
| | 24 hrs. | A. | .... | Sterile | Infinite | 20 | Infinite | |

This experiment is typical of a certain type encountered, in which the bile was germicidal for Eberthella typhi, but failed to kill the Gram-positive coccus. This organism, a yellow chromogen, which fermented dextrose and lactose but failed to liquefy gelatin, was frequently encountered in bile.

CASE II (No. 26).—White male.
Dosage, 20 cc. mercurochrome at 4.30 P.M.
Drainage, 10.30 A.M. next day. Eight tubes, of which Nos. 1, 2, 3, 4 and 8 were studied bacteriologically, as follows:

After centrifugalization four 1-cc. transfers of the supernatant fluid from each of the tubes studied were placed in small test tubes. One test tube

from each of the specimen tubes was inoculated with Staphylococcus aureus 209, one with Eberthella typhi, one with Flexner dysentery, and one with Streptococcus pyogenes. A large loop was used for these inoculations, which were made from eighteen-hour broth cultures—plain broth for all but the streptococcus which was transferred from blood broth. At once after inoculation 0.1 cc. was removed from each test tube and added to 9 cc. of melted, cooled agar. One cubic centimeter of this was transferred to 9 cc. of agar and both tubes were poured at once—plain agar being used except with the streptococcus for which blood agar was used. The results are summarized in the accompanying Table III. They show sterilization of Eberthella typhi by all specimens, and of Eberthella dysenteriæ Flexner by four specimens. Streptococcus pyogenes showed no complete sterilization but a reduction from over 200 colonies to 1 colony in one, to 20 in another, and so forth. The poorest results were obtained against Staphylococcus aureus, three test tubes showing no effect on this organism, one a slight reduction, and one a reduction to 1 colony, therefore even here there was some evidence of inhibitory action on bacterial growth.

**Roentgen Ray Evidence.** After we had done several experiments, the thought occurred that the Roentgen ray demonstration of the dye in the gall bladder would be interesting. Consequently several patients have had films made and we have been fortunate in obtaining shadows of the vesicle in a few instances. The presence of gas in the hepatic flexure spoiled the picture in several cases. The reproductions of Roentgen ray films may be of interest:

Fig. 1 shows the gall bladder of a normal man. Fig. 2 shows one of a patient with migraine, Fig. 3 is of a neurotic colored man. In these cases, a normal filling and emptying was obtained by the Graham test which in 1 case was done four days before the injection of mercurochrome and afterward in 2 cases. We were not able to obtain gall-bladder shadows in the cases in which this tetraiodophenolphthalein test did not show gall-bladder concentration.

In this connection it is of great interest to note that eight vesicles which did not cast a shadow with tetraiodophenolphthalein were able to retain mercurochrome and evacuate it the next morning.

**Immediate Clinical Results of Intravenous Medication.** We always informed patients that they should expect a reaction and were rarely wrong. The reaction may be anything from a mild diarrhea or nausea to a marked chill with fever, vomiting and diarrhea. At times they feel quite "knocked out."

Urine tests were made in 12 of these cases and in 3 we found a transient albuminuria. Since so much of the dye is excreted by the liver and withdrawn through the duodenal tube it is rather difficult to imagine how any real kidney damage could be brought about. Dr. Young and his staff are quite certain that they have never produced any kidney lesion by its administration.

In 1 case there were streaks of blood with the bowel movements which were very frequent. This lasted for about eighteen hours.

**Therapeutic Results of Intravenous Medication.** In this small group of cases we are not prepared to draw any definite conclusions.

However, as we have injected eight individuals who have had evident signs and symptoms, coupled with laboratory findings, of cholecystitis, it may be of interest to produce our data.

We have treated these 8 patients; 3 of them have been unimproved, 5 have been markedly helped or are symptomless several months after the second or third injection. Of the 3 that were not benefited 2 were women and received small amounts.

TABLE IV.—RESULTS FROM EIGHT CASES OF CHOLECYSTITIS.

| Case. | Sex. | Severity of symptoms. | No. of injections. | Amts. M/220 in cc. | Bacteriologic findings. | Mercury. | Results. |
|---|---|---|---|---|---|---|---|
| 18 | M. | ++++ | 2 | 20<br>20 | Sterilization<br>No inhibition | + to ++++ | Remarkable improvement; returned to work after absence of 3 mos. |
| 19 | M. | + | 3 | 20<br>20<br>20 | Inhibition<br>Sterilization<br>No inhibition | Not done<br>+ to ++++<br>Not done | Greatly improved. |
| 21 | F. | ++ | 1 | 12 | No inhibition | Not done | No improvement. |
| 22 | M. | ++ | 2 | 20<br>20 | No inhibition<br>Inhibition | 0<br>+ to ++ | After severe gall-bladder colic, no symptoms. |
| 23 | M. | +++ | 3 | 20<br>20<br>20 | Sterilization<br>No drainage<br>No drainage | Not done | 2 injections gave symptomatic cure; recurrence after 6 mos. |
| 32 | F. | ++ | 2 | 12<br>17 | No drainage<br>Sterilization | + to ++++ | Much better, no symptoms. |
| 33 | F. | ++ | 2 | 5<br>12<br>12 | No inhibition<br>Sterilization of B. typhosus | +<br>Not done | No improvement. |
| 34 | M. | + | 1 | 20 | Sterilization | + to ++++ | No improvement |

The frequent severity of the reaction is one of the commoner objections to the intravenous use of mercurochrome. As we have noted above, a reaction of some type is to be expected but never yet has a patient been unwilling to take a second or third injection.

**Animal Experiments.** To store mercurochrome in the gall bladders of dogs the same procedure was carried out as in human beings. They were given a fatty meal at noon, at 5.00 P.M. they received 8 cc. of 1-per cent mercurochrome by vein.

The next day at operation the contents of the gall bladder was withdrawn by syringe and bacteriologic and mercury tests similar to those done on human bile were carried out.

TABLE V.—DOG BILE.

| Specimen taken from dog. | Colonies 1 min. after inoculation with Eberthella typhi. | Colonies 24 hrs. after inoculation with Eberthella typhi. | Amount of mercury. |
|---|---|---|---|
| 20 hours after injection | Heavy growth of E. typhi | No E. typhi, 1 mold and moderate growth of Gram + b. | ++ |
| 4 days after injection | Heavy growth of typhi | Heavy growth of E. typhi | 0 |

Four days after the first operation the gall bladder was removed and the bile was again tested for its bactericidal property and mercury content. See Table V for results.

On another dog, the gall bladder was fixed in Zenker's solution after the mercurochromized bile was withdrawn. Microscopic sections were made, without staining the material, after a hemotoxylin and eosin stain, and after washing the section in ammonium sulphide. In no instance were we able to demonstrate the presence of mercury or any damage in the cells of the mucous membrane of the organ.

**Summary.** 1. After oral administration of mercurochrome to the point of salivation in 13 individuals: (*a*) The bile was never bactericidal or inhibitory and never contained visible traces of the dye. (*b*) The treatment had no alleviating effects upon the symptoms of 8 individuals with cholecystitis.

2. Following intravenous injection of mercurochrome in man, the dye may be demonstrated in the bile siphoned out through a duodenal tube in eighteen to twenty-three minutes.

3. This bile is bactericidal and contains mercury.

4. Eighteen to twenty hours after intravenous injection, mercurochrome may be obtained by duodenal drainage. It apparently can be stored in the gall bladder.

5. This bile is bactericidal and contains mercury.

6. Eight individuals with cholecystitis have received mercurochrome intravenously. Three were not helped; five are clinically cured and their bile specimens were sterile.

7. The gall bladders of dogs contain mercurochrome eighteen hours after intravenous injection.

8. This bile contains mercury and is bactericidal.

9. Due to storage of mercurochrome in the gall bladder it is possible to obtain its shadow in Roengen-ray films.

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# REVIEWS.

THE FUEL OF LIFE, EXPERIMENTAL STUDIES IN NORMAL AND DIABETIC ANIMALS. By JOHN JAMES RICKARD MACLEOD, M.B., LL.D., D.Sc., F.R.S., Professor of Physiology, University of Toronto, Canada. Pp. 147. Princeton, N. J.: Princeton University Press, 1928. Price, $2.50.

THIS volume comprises four lectures delivered by the author at Princeton University under the Lewis Clark Vanuxem Foundation. This book, as the author states, deals especially with the question as to whether fat as well as protein forms carbohydrate before being used as fuel. He states that "According to our view neither protein nor fat is burned by the muscles until it has been converted into carbohydrate or some related substance, mainly by the liver." He then proceeds to give a fine compilation of the more recent evidence which has to do with this question.

Like any debated subject those who favor the view that carbohydrate can be formed from fat will feel convinced. On the other hand, those opposed will, most probably, not find enough to change their views. This book, however, should be of value to those interested, as it contains the current data bearing on this subject.

L. J.

THE PRESSURE PULSES IN THE CARDIOVASCULAR SYSTEM. By CARL J. WIGGERS, Professor of Physiology, Western Reserve University, Cleveland, Ohio. Pp. 200; 48 illustrations. New York: Longmans, Green & Co., 1928. Price, $5.00.

THE author has produced an admirable monograph on this subject with which he has been himself so closely associated. The original work of Frank is well reviewed and a useful summary of Frank's equations for estimating and improving manometer efficiency is included. The whole subject is reviewed in detail from the point of view of establishing the facts without any long controversial discussion as to causes. There is little or no cause for criticism, though one may regret that Frank's equations for the optimum diameter of the tubing construction of a manometer is not included in the description of technical methods. It is an excellent book and should prove very useful.

H. B.

MEDICAL AND ALLIED TOPICS IN LATIN POETRY. By HEINRICH OPPENHEIMER, D. LIT., LL.D., PH.D. (LOND.), M.D. (HEIDELBERG), M.R.C.P. (LOND.), of the Middle Temple, Barrister-at-Law. Pp. 445. London: John Bale, Sons and Danielsson, Ltd., 1928. Price, 30 shillings.

A WAR-TIME enemy alien in England, the "innocent victim of social and—*horribile dictu*—to some extent of professional ostracism," the author sought comfort in the classical writers and soon found much medical material therein. This he has now presented, classified under some twenty-four such headings as Medical Sociology, Biology, Surgery, Insanity, Cosmetics, etc., the bulk of the text being quotations, interspersed with pithy, thumb-nail introductions two or three lines in length. A list of passages quoted, of translations, and a good index add to the usefulness of the book. Though the author denies any claim to have produced either a scientific work or a serious contribution to Roman medical history, others may fairly consider that he has done both. Fortunately, too, the author has included footnote translations of the Latin passages. In these non-classical days, a reversed position would have facilitated the progress of most readers. The alien is to be congratulated, also the publisher, who in happier times has brought out the alien's book. E. K.

THE HARVEY LECTURES. DELIVERED UNDER THE AUSPICES OF THE HARVEY SOCIETY OF NEW YORK, 1927–1928. By DR. EDWARD FRANCIS, DR. FRANK C. MANN, DR. CARL F. CORI, DR. WALLACE O. FENN, DR. GEORGE R. MINOT, DR. E. S. LONDON, DR. THOMAS ADDIS, and DR. ALFRED E. COHN. Series XXIII. Pp. 280; 39 illustrations. Baltimore: The Williams & Wilkins Company, 1928. Price, $4.00.

EIGHT discussions by the above noted distinguished physicians of these topics: Present Knowledge of Tularemia; The Relation of the Liver to Metabolism; Influence of Insulin and Epinephrine on Sugar in the Animal Body; Metabolism of Nerves; Treatment of Pernicious Anemia; Experimental Fistulæ of Bloodvessels; The Renal Lesion in Bright's Disease; Development of the Harveian Circulation. R. K.

MALARIA PROBLEMS. By FREDERICK L. HOFFMAN, LL.D., Consulting Statistician, Prudential Insurance Company. Pp. 207. Privately printed, 1928.

THERE have been collected within one cover thirteen reprinted articles by the author, dealing with the public-health and economic

aspects of malaria, that have appeared in various journals since 1916, and a concluding 25-page statement of recent progress in malaria eradication in all parts of the world. The work serves well to visualize both the national and international phases of a problem that is of a particularly great importance in this country, its tropical possessions and its southern neighbors. R. K.

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HORMONE UND INNERE SEKRETION. By DR. FRITZ LAQUER. Band XIX of "Wissenschaftliche Forschungsberichte." Pp. 136. Dresden and Leipzig: Theodor Steinkopff, 1928.

ONE of a series of "Reports on Scientific Researches:" surveys of the literature that has appeared in various scientific fields since 1914. In the present volume, No. XIX, dealing with hormones and internal secretion, the author has attempted a critical review based on over 1200 publications that have appeared from 1915 to 1927 inclusive, and he has succeeded remarkably well. R. K.

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CHILD HEALTH AND CHARACTER. By ELIZABETH M. SLOAN CHESSER, M.D. Pp. 204. New York: Oxford University Press, American Branch, 1927. Price, $1.50.

ON the postulate that "as a knowledge of hygiene is the basis of health, so also in the study and application of psychology lies the great hope of increasing human happiness," "this little book has been written to help mothers to understand some of the health problems and psychologic problems from infancy to adolescence." The author has succeeded unusually well in presenting the psychologic material, especially in the chapters entitled, "The Toddler," "Child Psychology," "The Study of Character," "The Difficult Child," "Boys and Games," and "Adolescence." "Diet and the Health of the Child," "Sunlight and Health" and "Adolescence" are adequately presented, although the style begins to grow prolix, and the author at times inveighs a bit unduly against the carbohydrates: "very little wholemeal bread, no biscuits, cakes or rusks, nor rice or sago puddings." Hygienic principles and some rudimentary medical information are presented under "The Importance of Prevention of Illness," "Infectious Diseases in Childhood," "Sickness in the Nursery." Here again there is some unnecessary repetition, and, furthermore, the author has missed a golden opportunity to tell mothers something about prophylaxis against diphtheria, scarlet fever and smallpox: the Schick and Dick Tests, toxin-antitoxin and vaccination. The book can nevertheless be highly recommended to the lay reader. R. K.

PRESCRIBING OCCUPATIONAL THERAPY. By WILLIAM RUSH DUNTON, JR., B.S., A.M., M.D., Instructor in Psychiatry, Johns Hopkins University. Pp. 144. Springfield, Illinois and Baltimore, Maryland: Charles C. Thomas, 1928. Price, cloth, $2.10; paper, $1.35.

WHILE most physicians realize the importance of occupational therapy in one condition or another, it is safe to say that few of them have a clear understanding of the indications for and methods of applying this important branch of treatment. The subject receives no systematic presentation in medical curricula and the literature, chiefly a recent one, is largely restricted to special fields. This little book in Part I gives a concise statement of the general principles involved, and in Part II takes up the special application of occupational therapy to patients with mental disorders, general medical, surgical, orthopedic, cardiac, and tuberculous conditions, to children and to those who are bedfast. There are numerous references to collateral reading for those who desire more detail. The book should be particularly useful to the busy physician and the medical student. R. K.

## NEW BOOKS.

*Recent Advances in Neurology.** By W. RUSSELL BRAIN, M.A., D.M. (OXON.), M.R.C.P. (LOND.). Pp. 412; 38 illustrations. Philadelphia: P. Blakiston's Son & Co., 1929. Price, $3.50.

*Report of the International Conference on Cancer, London, July* 17–20, 1928.* Pp. 588. New York: William Wood and Company, 1929. Price, $12.00.

*You and the Doctor.** By JOHN B. HAWES, 2D, M.D. Pp. 181. Boston and New York: Houghton, Mifflin Company, 1929. Price, $2.00.

*Medical Clinics of North America.* Southern Interurban Clinical Club Number, March 1929, Volume xii, No. 5. Pp. 306; 40 illustrations. Philadelphia: W. B. Saunders Company, 1929.

*The Medical Department of the United States Army in the World War. Volume IV. Activities Concerning Mobilization Camps and Ports of Embarkation.* Pp. 494. Washington: U. S. Government Printing Office, 1928.

*The Biochemistry of the Amino Acids.** By H. H. MITCHELL and T. S. HAMILTON. Pp. 619; 18 illustrations. New York: Chemical Catalog Company, 1929. Price, $9.50.

* Reviews followed by an asterisk will appear in a later number.

# PROGRESS

OF

# MEDICAL SCIENCE

## MEDICINE

UNDER THE CHARGE OF

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**The Clinical Significance of Cardiac Asthma: Review of 250 Cases.**—The syndrome of acute shortness of breath, paroxysmal in type, associated with a tendency to occur particularly at night, though sometimes following exercise, accompanied by a sense of suffocation, cough and sputum, has interested physiologists and cardiologists for a long time. The mechanism of production of this phenomenon, so satisfactorily relieved by morphin, has been a subject of discussion for some years, but no satisfactory evidence has been brought forth to explain completely the genesis of the symptom. PALMER and WHITE (*J. Am. Med. Assn.*, 1929, **92**, 431), as the result of the study of a group of 250 patients, have this to say. A serious strain on the heart in all cases, involving chiefly the left ventricle and associated with other signs and symptoms of heart failure, especially the left ventricle, the attacks coming on when the patient is asleep in the recumbent position, lasting not more than half an hour, as a rule, associated with coughing up of blood and the prevention of the attacks by digitalization and rest are the high points which enable them to suggest that left ventricular strain and failure cause, with increased bloodflow, a stasis of blood in the pulmonary circulation, the right ventricle sending on too much blood for the left ventricle to take care of. Gradually this accumulation of blood in the pulmonary circuit increases, until by reflex stimulation the attack of asthmatic breathing is induced and the patient is awakened. By assuming the upright position the statis and strain on the left ventricle are reduced and recovery takes place. Morphin reduces the irritability of the respiratory centers, as well as other nerve centers, aiding the circulation by relieving the nervous strain. The authors summarize their analysis of the patients studied. The great majority were males and all but 14 were over forty years of age. The average duration of life was 1.4 years after the first attack of cardiac asthma, although the largest number of cases, 187, were found in patients with coronary disease, hypertension, or both, and the highest relative percentage occurred in syphilitic heart disease and in chronic nephritis.

**The Relations of Syphilis and Diabetes to One Another.**—The relationship between syphilis and diabetes mellitus has been a matter of discussion and controversy for nearly seventy years writes I. I. LEMANN (*Am. J. Syphilis*, 1929, **13**, 70), who has reviewed the extensive literature on the subject from 1858 until the present time. The literature is gone over: (1) From the point of view of the cases of diabetes mellitus apparently due to syphilis; (2) the evidence for or against syphilis as an etiologic factor; (3) the rôle played by syphilis as a complication of diabetes; and, (4) the rôle played by diabetes as a complication of syphilis. Considering the very large number of patients who suffer from syphilis in this country and the very large number of diabetics, it might seem that there was some relationship between the two conditions, but that this evidence is most indefinite and the possibility is remote is shown by this study of the two diseases. There is not any conclusive and definite evidence that diabetes can be caused by cerebral syphilis. There is very little evidence and there are very few cases reported in which syphilis is the cause of true pancreatic diseases as proved at autopsy and only a comparatively few cases in which we may reasonably assume that diabetes might be due to syphilis. If, then, there is some connection between the two diseases, most assuredly the rôle of syphilis is a distinctly minor one in the genesis of diabetes. In an individual who has diabetes or in a person who has syphilis and becomes diabetic, the prognosis is increasingly grave except in the very occasional instances where the syphilis is responsible for the diabetes, under which circumstances the prognosis is better than in the non-syphilitic. Last, in his survey of the literature and from his personal experience, Lemann shows that a diabetic with a coexisting syphilis is probably more prone to artificial disease and more prone to gangrene, consequently, than is the diabetic without this complication.

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**Stereoscopic Radiograph of the Coronary System.**—In a study of the minute anatomy of the vascular system there is much to present a clear picture of the genesis of many conditions which are the primary importance to the clinician. JOHN S. CAMPBELL (*Quart. J. Med.*, 1929, **86**, 247) describes a method by which it is possible to make stereoscopic radiograms of the coronary system. The details of the technique need not be enumerated nor is it possible to discuss in detail the distribution of the coronary arteries. Suffice it to say that marked variations in the anatomic distributions of the coronary vessels are frequent and these are important in the clinical aspects of coronary disease. Anastomoses are peculiarly rich and are of great importance in preserving cardiac musculature, particularly in relation to coronary infarction. So rich is the anastomosis in many cases that coronary disease by this method of study has been found to be quite common without being suspected by the medical attendant. The heart is able to adapt itself to very marked alterations in the lumen of the vessels or the sources of its supply provided the lesion is not too sudden in onset or too extensive in degree. Incidentally, in relation to the clinical manifestations of coronary thrombosis and cardiac infarction, is the change produced by age in the coronary circulation. Marked tortuosity is apparent in the small vessels and the anastomoses seem to be considerably diminished on the right side, whereas on the left side there is an increase.

# SURGERY

UNDER THE CHARGE OF

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**Stricture of the Male Urethra.**—CAMPBELL (*Ann. Surg.*, 1929, **89**, 379) says that urethral stricture in the male is of prime importance among surgical lesions of the urinary tract. Over 90 per cent of urethral strictures are of inflammatory origin. Nearly all follow gonococcic urethritis. Since columnar and cylindrical epithelium favor gonococcus growth and squamous epithelium is resistant to this infection, inflammatory stricture is common to the anterior and bulbous urethra, but rarely found in the membranous portion. The latter, however, is the site of most traumatic strictures, the straddle injuries of the perineum. Improper treatment of the antecedent urethritis accounts for most gonorrheal strictures, even though the lesion may give no symptoms until twenty years later. Stricture depends on the severity of the urethritis, rather than on the duration. The majority of inflammatory strictures are clinically multiple, though pathologically they may be single. Traumatic strictures are usually single. The symptoms of stricture are varied, and may be present many years before acute local inflammation precipitates search of medical relief. Alteration in the size of the urinary stream, terminal dribbling, dysuria, frequency of urination, hematuria and an intermittent glut are perhaps most commonly observed. Urine shreds are always present with stricture. Urinalysis frequently discloses blood. Failure to respond to dilatation and certain complicating infections are the indications for operation. For deeper strictures perineal section must usually be performed. When this is done a perineal bladder tube should always be used. Preservation of free urinary drainage, free evacuation of the bowels and forced fluid intake sums up the immediate postoperative care. Numerous postoperative complications may develop, many of which are potentially fatal. The most important of these are urosepsis, hemorrhage and pneumonia.

**The Treatment of Intestinal Obstruction.**—ORR and HADEN (*Ann. Surg.*, 1929, **89**, 354) state that, from the operative standpoint, obstruction of the small bowel may be divided into early and late simple obstruction and obstruction associated with circulatory disturbance or gangrene. In the early cases of simple obstruction immediate operation can be done with safety. In the late cases of simple obstruction operation should never be done without preliminary treatment of the dehydration and hypocloremia. In cases complicated by strangulation of the gut or gangrene early operation is imperative, but may with great benefit be preceded by salt-solution treatment. Dehydration and hypocloremia play major rôles in death due to intestinal obstruc-

tion. In every case sufficient salt solution should be given as rapidly as possible to correct these two conditions. Distilled water should never be used alone. Experimental evidence has shown it to be not only useless, but dangerous when introduced in large quantities under the skin or by enterostomy opening. Intravenous administration of glucose in 10 to 25 per cent solution is of great value in furnishing energy. It may be given with the salt solution. Enterostomy as a preliminary operative treatment is of undoubted value in selected cases. It should not be depended upon to the exclusion of water and salt. Treatment of intestinal obstruction with Welch bacillus antitoxin or human bile by rectum requires further investigation to establish its value.

## THERAPEUTICS

UNDER THE CHARGE OF

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**The Treatment of Endocarditis Lenta by Cauterization at the "Site of Election."**—Following up the original observations of Bier, CONSTANTIN V. BRAMANN (*Medicinische Klinik*, 1929, **25**, 12), his assistant, reports upon the results of subcutaneous cauterization over the precordial area as observed in a group of 28 patients with endocarditis lenta. These patients are divided into two groups, an earlier one of 12 patients most of whom were in good general condition or still had mild grades of bacterial endocarditis, and a later group of 16 patients the majority of whom were in a very advanced stage. Of the first group 6 showed marked improvement, in only one of whom, however, was this improvement lasting. In the second group of 16 the majority died within three to six months after treatment. In 6 of them death was preceded, however, by a fairly prolonged period of improvement. Two patients with septic, malignant endocarditis, were apparently entirely cured by the treatment. The technique of the method consists in the creation of a subcutaneous pouch over the whole precordial area. A flatly curved incision is made through the skin and subcutaneous tissues over the upper portion of the chest under local anesthesia. Through this opening the tissues are elevated from the chest wall over a wide area and the entire inner surface of the pouch is carefully burned with a thermocautery, the margins of the incision alone being lightly burned. The flap is then sewed tightly into place. Marked pain is not produced as a sequel to this procedure. Elevation of temperature follows two or

three days after the operation but the fever usually subsides by about the eighth day. In some cases a secondary rise is observed. The operation is followed in many cases by marked increase in the appetite and in the ability to sleep, both of which often continue for several months. A small collection of fluid may accumulate in the sack but this is usually absorbed fairly readily. In the cases in which absorption is slow improvement seems to be more marked. Embolic phenomena disappeared for periods of months in 3 patients. Postmortem examination failed to reveal any direct influence upon the endocarditic lesion. The author believes that although the method cannot yet be regarded as promising a cure it is nevertheless of marked value by reason of its capacity to relieve symptoms, to improve health and to prolong life in these patients. It also seems probable that one of the patients is permanently cured although it is yet too soon to be certain. Repeated application of the treatment may give better results and the same may be expected when earlier cases are treated. All of those in these two series had been under intensive treatment by the usual medical methods and had failed to show any clinical improvement. The author suggests finally that the method may be a useful adjuvant to the usual medical methods of therapy.

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**Experimental and Clinical Observations on Dodekamethylendiguanidin (Synthalin B).**—In the course of their investigations on the action of guanidin derivatives NOTHMANN and WAGNER (*Klin. Wchnschr.*, 1928, **7**, 1996) observed that the toxic as well as the therapeutic actions of these preparations were diminished and delayed by the addition of methyl radicals. In the present communication, they report on a series of experiments with dodekamethylendiguanidin which they have named synthalin B. Upon animals they find it distinctly slower than synthalin, dekamethylendiguanidin, in its capacity to reduce the blood sugar. It is also materially less toxic although its toxic actions are qualitatively the same as those of synthalin. They have treated 150 diabetic patients with this new preparation and find, similarly, that its actions are the same in the human as those of synthalin differing only in intensity and rapidity of development. They recommend that the initial dose be 5 mg. three times a day and that this be raised within four or five days to a maximal dose of 15 mg. three times a day. They also recommend interruption of administration for one or two days after the drug has been administered daily for three or four days. These doses will care for from 30 to 50 gm. of sugar. The action is so slow, however, that a reduction in glycosuria often does not appear before the third day of the first course. The drug may be administered almost indefinitely upon the foregoing scheme. Its action in diminishing acidosis and acetonuria are similar to those of synthalin. Like synthalin, however, it is devoid of the trophic actions of insulin. Hence in greatly undernourished or in exceedingly enfeebled patients the strength and nutrition of the patient should be restored by the administration of insulin and synthalin B may then be used for continued treatment. While the several toxic actions of synthalin do appear with synthalin B the likelihood of their development is very much less and if they do develop they are of milder grade. No disturbance of liver function has been observed by the authors following its use.

# PEDIATRICS

UNDER THE CHARGE OF

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**The Monocyte in Active Tuberculosis.**—BLACKFAN and DIAMOND (*Am. J. Dis. Child.*, 1929, **37**, 233) found in their studies that 8 patients with steadily increasing monocyte-lymphocyte ratio died. In 3 patients, after an initial rise in the monocyte-lymphocyte ratio, the ratio was reversed and approached the normal ratio for the age. As the number of lymphocytes rose, it was noticed that the large young lymphocytes predominated. The changes in the blood preceded and pointed to the general improvement in the patients' condition. From their observations they feel that the degree of activity in tuberculosis is reflected in the peripheral blood of infants and children. A high ratio and the presence of epithelioid cells usually mean an active tuberculous infection. An increasing monocyte-lymphocyte ratio and the persistence of a high absolute monocyte count signify extension of the process. Reversal of the ratio or a fall in monocytes and an increase in lymphocytes denotes healing lesions. In cases in which the diagnosis is questionable a study of the blood by the supravital technique may lead to a correct diagnosis. After establishment of the diagnosis supravital studies of the blood may be of prognostic value in indicating whether the lesion is progressing or undergoing regression.

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**The Routine Use of the Vitamin B Factor in Infant Feeding.**—DENNETT (*J. Am. Med. Assn.*, 1929, **92**, 769) agrees with Macy and Hoobler, that cows' milk and sometimes breast milk does not contain the most satisfactory quantity of vitamin B; therefore some vitamin B besides that contained in cows' milk should be added as a routine procedure to the diet of all bottle-fed babies in much the same manner as cod-liver oil and orange juice are universally used. One-third ounces by weight or one level tablespoonful of wheat-germ sugar provides as much of the antineuritic factor as one quart of milk and as much of the antipellagric factor as ten ounces of milk. This sugar is most conveniently used, is more palatable and is more easily available than these. He feels that from one to three tablespoonfuls should be given daily to every bottle-fed infant throughout the first year of life.

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**Acid-base Metabolism.**—SCHOENTHAL (*Am. J. Dis. Child.*, 1929, **37**, 244) studied the effects of the administration of sodium chloride and of restriction of water on the total metabolism and the acid-base equilibrium of the body. He found that the administration of sodium chloride in infants in addition to a regular diet and in the absence of water restriction resulted in an increase in the chloride concentration of the plasma, a moderate reduction of plasma bicarbonate, a tendency of the plasma reaction to become acid, changes in the water content as evidenced by protein concentration, a constant increase in excretion

of bicarbonate in the urine with a shift in reaction toward alkalinity, a relative increase in excretion of fixed base over fixed acid, a decrease in György coefficient in the urine and usually a slight or moderate febrile reaction. The feeding of a concentrated food with the restriction of water produced the same changes in the metabolism as did the administration of sodium chloride. The blood concentration was marked and fever was high and symptoms characteristic of alimentary intoxication were observed. These results indicate the possible danger of the indiscriminate use of salt solution in children suffering from anhydremia. The effect of this administration may be to increase the degree of acidosis and to prevent restriction of a normal acid-base equilibrium.

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**The Physical and Mental Growth of Breast-fed and Artificially-fed Infants.**—Hofer and Hardy (*J. Am. Med. Assn.*, 1929, **92**, 615) analyzed the infant-feeding history of 383 elementary school children. They found that children who were artificially fed were, on the whole, physically and mentally inferior to the breast-fed. Except for height they ranked lowest in all the physical traits measured. From the standpoint of nutritional standards they were the poorest nourished group. They were the most susceptible to diseases of childhood. They were the slowest of all groups in learning to walk and talk. In mental development the artificially-fed ranked next to the lowest and the lowest were those breast-fed from ten to twenty months of age. Of the children with superior intelligence, the smallest percentage was found in the artificially-fed group, and not a child of this group was classified as being exceptionally bright. In considering the two types of artificial foods most commonly used in these children, modified cows' milk seemed to be a more satisfactory food from the standpoint of later development than unsweetened evaporated milk. The children who were breast-fed from four to nine months were definitely superior physically and mentally than all the other groups. Children who were fed exclusively on breast milk longer than nine months, although they seemed to develop at a normal rate physically, were the lowest group in mental development.

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**Observations on the Use of Irradiated Ergosterol in Active Rickets.**—Sobel and Claman (*Arch. Pediat.*, 1929, **46**, 1) administered ergosterol and found there was a decided improvement in the general well being, the appetite, the digestion, the color, the general behavior, the animation and muscle tone. Craniotabes disappeared in two weeks and open anterior fontanelles diminished in size from four to two fingers in six weeks. The laboratory findings demonstrated a definite increase in the blood phosphorus to a normal level. Roentgenography showed a progressive calcification at the epiphyses and diminution of cupping and fraying. The irradiated ergosterol which was used was a 1 per cent solution of a commercial product not on the market. At first, large doses were used, but later relatively smaller doses were tried, and the results with these equalled those obtained with the larger doses. No untoward effects were noted either in large or small doses. They felt that the irradiated ergosterol is a powerful and reliable specific agent for active rickets, but as it is not biologically standardized it is safer to use smaller rather than larger doses. They feel that from the stand-

point of vitamin D it promises to supplant cod-liver oil and ultraviolet therapy, although cod-liver oil will still find its usefulness for its fat vitamin A content and ultraviolet therapy will be used for the general tonic effect and improvement of general metabolism. It was noted that in the fractures occurring in rachitic infants, callous formation and calcification were hastened by this therapy. It was used in a limited number of premature babies and also for the prevention of rickets in a small number of cases and the authors feel that it will replace cod-liver oil for these purposes. They feel that in the treatment of tetany, irradiated ergosterol will probably replace the use of calcium salts and parathyroid extract because of its greater ease of administration.

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**The Relation of the Altitude of the Sun to its Antirachitic Effect.**—TISDALL and BROWN (*J. Am. Med. Assn.*, 1929, **92**, 860) say that a marked increase occurs in the antirachitic effect of sunshine when the sun reaches an altitude of 35 degrees or more. A study of the geographic distribution of rickets shows that rickets is uncommon or exists chiefly in a mild form in those places where the minimum seasonal altitude of the sun is not below 35 degrees. On the other hand, severe rickets is met principally in those cities where the altitude of the sun is below 35 degrees for some months of the year. The period of the year during which rickets will probably develop can be calculated for any city. The duration of this period may be altered by prevention of exposure of patients to highly effective sunshine on account of of unfavorable spring weather or other factors.

## DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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**Absorption of Salicylic Acid by the Human Skin.**—LESLIE-ROBERTS (*Brit. J. Dermat. and Syph.*, 1928, **40**, 325) claims that absorption of drugs by the human skin has been demonstrated in the case of nicotin, aconite (Macht) and atropin. Friction brings about the absorption of mercury; but the number of other drugs actually absorbed without injury to the skin is small. In 62 cases studied by the author for absorption of pure synthetic salicylic acid through the skin, using a new colorimetric method, 48 showed the presence of the drug in the urine. Alcohol, water and vaseline were used as vehicles, and the concentration of the drug in the vehicle ranged from 3 to 50 per cent.

Definite evidence of absorption from areas as small as 1 to 2 square inches with a 50 per cent ointment were obtained. In two and a half hours 0.416 per cent salicylic acid was obtained in the urine from an area 4 by 5 inches. Alcohol favors penetration in proportion to its concentration. The absorption of the drug from aqueous solution reverses previous conclusions as to the absorption by the skin of drugs dissolved in this medium. The colloids of the connective tissue absorb the drug. Solid keratin, while impervious to salicylic acid, acts by an extraordinary adsorbing power, permitting a supersaturated solution to form on the skin surface. It is suggested that cholesterols are instrumental in the transposition of the drug.

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**Histochemical Studies on the Localization of Lipoids in the Skin.**—St. Wahl's (*Arch. f. Dermat. u. Syph.*, 1928, **156**, 303) studies indicate that lipoids are most abundant in the skin of the scalp and axillæ, and least abundant in the hairless regions. They are localized largely in the sebaceous glands and epidermis and least abundant in the sweat glands and hair shafts. The observations are of interest in view of Jaffé's theory that cholesterin and lipoids are necessary to the growth and nutrition of hair. The author's observations do not support the belief that the skins of patients with high cholesteremia have a high cutaneous cholesterol or lipoid content.

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**Studies in Agglutinin Titer for Staphylococcus Through Specific and Nonspecific Vaccine Injection.**—Michael (*Arch. f. Derm. u. Syph.*, 1928, **156**, 260) finds that normal blood serum agglutinates staphylococci in a concentration of 1 to 10 to 1 to 40. In furunculosis this concentration decreases to 1 to 1000 to 1 to 2000. The intracutaneous or intravenous injection of vaccine raises the titer to from 1 to 2000 to 1 to 10,000, whereas the subcutaneous injection of the vaccine raises it only to 1 to 400 to 1 to 800. The inflammatory reaction of the skin is believed to be responsible for the antibody formation. The effect is not specific, for similar methods of injection, using arthigon in gonorrheic patients, give rise to a similar increase in titer of serum agglutinins for staphylococci.

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**Does the Gennerich-Milian Reactivation of the Wassermann Reaction Exist?**—Boas and Portman (*Arch. f. Derm. u. Syph.*, 1928, **156**, 308) find that by running a series of controls which had not received a preliminary salvarsan injection, parallel to a series which did, no true provocative or activating effect could be demonstrated, the fluctuations in the series of tests (Kahn and Meinecke techniques included) being almost identical in both series.

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**Hypersensitiveness to Chinons.**—Mayer (*Arch. f. Derm. u. Syph.*, 1928, **156**, 331) believes he has traced the sensitization phenomena involved in fur dye and photographer's dermatitis to the chinon group in these compounds. Azo dyes are reduced by the living cell and thus act in cell respiration as oxidation equivalents. Aminophenol and phenylendiamin are intermediate stages in the formation of the chinons, which are the true offenders and act as the "antigens" in the cutaneous reactions.

# GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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**Vaginal Hysterectomy.**—Although there are many gynecologists in this country who frequently perform hysterectomy by the vaginal route, it must be admitted that by far the larger number of hysterectomies are performed through an abdominal incision. Those who routinely perform abdominal hysterectomy probably often wonder why the vaginal route would be selected by any surgeon as the method of choice. For the benefit of these men, let us review briefly the article by PETIT (*Am. J. Surg.*, 1928, **5**, 252) of Paris, who reports a series of 123 consecutive vaginal hysterectomies with no mortality. He performs the operation under visual control without the use of clamps. The advantages which he claims for this method are that it produces a minimum of shock, reduces the danger of infection, simplifies the postoperative course, produces no abdominal scar, reduces the likelihood of the production of adhesions and reduces the time consumed by the operation. He believes that this type of operation is indicated in patients of advanced age or in a cachectic condition, especially in patients who have myomas of average size or total prolapsus after the menopause. The vaginal route is contraindicated, however, when the myoma is of excessive size or in cases in which myomectomy should be performed and also where there are extensive adhesions or coincident disease of the appendix.

**Comparison of Salpingography with Tubal Insufflation.**—The question has undoubtedly arisen in the minds of many conservative practitioners as to the relative merits and dangers of visualization of the Fallopian tubes by means of the Roentgen ray after the injection of iodized oil and the more simple peruterine tubal insufflation with carbon dioxid gas. Probably no gynecologist is more qualified to express an opinion on this subject than RUBIN (*Radiology*, 1928, **11**, 115), who has been identified with this type of work for many years and for whom the latter test is named. He states that the chief value of lipiodol in gynecology is the aid it offers in radiographing the point of obstruction in the tube and of distinguishing submucous myomata of the uterus. Its disadvantages may be briefly stated. It remains for a long time in the sealed tube and in the peritoneum. In some cases he has found it in the tube over six months after its introduction. The patient should be warned of the presence of the lipiodol because it can cause confusion in case a ureteral stone is suspected. It may cause serious irritation and it

requires two workers, an expert roentgenologist and a gynecologist. It is not infallible, since when it fails to pass the tubes into the peritoneal cavity it does not necessarily indicate tubal impaction but this may be due to an insufficient amount having been injected for that particular case or spasm may intercept it at the uterine horn. When only the uterine cavity is outlined by the lipiodol it is impossible to say whether the tubes are obliterated throughout or only at the intramural portion. On the other hand, carbon dioxid insufflation demonstrates tubal patency as well as nonpatency. The gas is rapidly resorbed and leaves no trace in the peritoneal cavity. It is practically an innocuous procedure, simpler to perform and less troublesome to the patient than the lipiodol injection and can be repeated with greater safety. It is an office procedure without risk when carefully carried out, requiring but one operator. Its diagnostic value with respect to tubal closure is equal to lipiodol and the test can be repeated at stated intervals with the greatest simplicity. With increasing experience it enables one to diagnosticate the important points of obstruction in the tube lumen. It is superior to lipiodol in demonstrating tubal spasm, which can be graphically recorded by the kymograph. In doubtful cases and in those where operative relief of tubal obstruction is desired, hysterosalpingography may be resorted to. The contraindications are the same for both methods and in those selected cases where they are combined.

## OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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(*Concluded from April issue.*)

**"Aspiration" Experiments.**—For many centuries the conception of Hippocrates—that aspiration of blood and mucus is the cause of pulmonary abscess—was accepted generally; and there seems to have been little or no doubt as to the aspiratory origin of postoperative abscess of lung in the minds of the older surgeons, who based their opinions largely on clinical observations. In view of this tradition, it is interesting to note that the early endeavors to create experimental pulmonary abscess by means of intratracheal inoculation were unsuccessful. (Aschner,[38] Lambert and Miller[6] and Cutler and others.[11,10,23])

Kline[39] was able to cause gangrene of the lungs of guinea pigs and rabbits by the intrabronchial instillation of fusospirochetal-containing material from a carious tooth. He interpreted his results as indicating that the aspiration of these bacteria from oral lesions of human beings may lead to a gangrenous process of the pulmonary tissue. Later, Kline[40] emphasized the importance of differentiating *gangrene* from *abscess.*

It remained for Smith[19] to induce abscesses in the lungs of mice, guinea pigs and rabbits by the intratracheal injection of bloody material obtained from the teeth of patients suffering with moderately severe pyorrhea. Pointing out that lung abscesses in man commonly contain two or more of such bacterial types as spirochetes, fusiform bacilli, cocci or vibrios, Smith concluded that infected material from the mouth accounted for most instances of pulmonary abscess.

Interpreting the absence of postoperative lung abscess in 3500 tonsillectomies—performed under light ether anesthesia and with rigid precautions to prevent aspiration of blood and mucus—as an argument favoring the aspiratory route of infection, Crowe and Scarff,[13] after repeated trials, succeeded in producing chronic lung abscesses in dogs by the introduction through a bronchoscope of a pledget of cotton saturated with fresh scrapings from human pyorrheal cavities. Analogous pulmonary lesions were obtained in two dogs following the placing of similar material in a frontal sinus. Inasmuch as the use of other bacteria failed to induce the same reaction, the authors suggest that the spirochetes in the pyorrheal lesions may have a specific rôle in the formation of abscesses of lung.

Simultaneously, Allen[41] reported the reproduction of multiple abscesses in canine lungs following the instillation into the bronchi of warm pus from patients with chronic pulmonary abscesses. Moreover, the author learned that obstruction of a bronchus was an important factor in the causation of the abscesses.

Lately, Joannides,[42] by introducing an admixture of fresh blood and human pulmonary abscess sputum into the bronchi of fourteen dogs, induced abscesses in ten of them. He considers as factors of great import in the production of pulmonary suppuration: (1) the abolition of the pharyngeal and cough reflexes in general anesthesia; (2) the presence of mucus or blood in the mouth during anesthesia; (3) the presence of "fuso-spirochætæ" in the buccal cavity; (4) the presence of chronic infection in the nose, mouth and paranasal sinuses; (5) the physical properties of the aspirated material; (6) the action of the cilia which clear the trachea and bronchi by rhythmic movement; (7) the specific immunity in the lung against certain bacteria, as for example staphylococci. Joannides agrees with Allen[41] and Myerson[43,44] that failure to expel aspirated material is more important than the aspiration itself and cites some recent investigations by Pilot,[45] who succeeded in producing abscesses in lungs of rabbits by intratracheal inoculation of fusospirochetal-laden material, which was caused to be retained there by the use of lipiodol.

Practically all of these experiments were performed on animals, anesthetized with ether. The influence of ether narcosis as a contributing factor to postoperative pulmonic infections is an old clinical observation and has been confirmed experimentally by Hoelscher,[46] who found previously-stained oral secretions, capable of producing pneumonitis, to be constantly present in the tracheobronchial tree of etherized animals. Corper[47] and his associates[48] observed that, under etherization, nasally-instilled fluids were inhaled readily by dogs and rabbits placed in a horizontal plane, whereas such aspiration did not occur in nonanesthetized animals. Furthermore, the recent experiments of Lemon[49] on etherized dogs showed that dyes, or barium suspension,

slowly administered orally, were drawn into the lower air passages except when the head of the animal was at least 28.75 cm. lower than the feet; and that, in accordance with Corper's[47] findings, aspiration could not be demonstrated in nonetherized dogs. Lemon concludes that "postoperative pulmonary infections may be explained, in part at least, as a result of infection carried to the lungs in oral secretion, which has been aspirated by the force of the air current when the chest expands, in patients whose protective mechanism has been disturbed"—a point also emphasized by Myerson,[43,44] Allen,[41] Joannides[42] and Pilot.[45] These results are of interest when compared with those of Laughlen[50] who found a peculiar microscopic cellular reaction to intrabronchial droplets of liquid albolene in the lungs of infants dying of bronchopneumonia. The albolene had been placed into the nares as a routine procedure. In addition, Laughlen was able to reproduce a similar pathologic picture experimentally in animals. Intructive observations have been made on two occasions by Myerson,[43,51] by Daily and Daily,[52] and by Vail,[53] all of whom, by bronchoscopic examination of etherized persons immediately after tonsillectomy, found blood in the tracheobronchial tract in 79, 76, 78 and 62 per cent of their cases, respectively. On the other hand, Herb's[14] study of the effects of anesthesia on the lungs led her to believe that under ordinary conditions properly administered ether is not any more likely to produce pulmonary complications than a local anesthetic.

Evidently believing that local anesthesia precludes or minimizes the possibility of aspiration, advocates of the "embolic" theory have pointed out that posttonsillectomic abscesses of lung have been reported in as high as 19.3 per cent of cases operated upon with the aid of a local anesthetic (Moore[16]); and that in some clinics (Gottstein,[54] Henle[55] and Mikulicz[22]) more pulmonary complications occurred with local than with general anesthesia.

Contrariwise, Ochsner and Nesbit[56] have demonstrated that local anesthesia did interfere with the normal protective reflexes in over 600 cases of bronchography, done according to the "passive technic," and that aspiration did occur following the cocainization of the pharynx. Surmising that the same condition might prevail in local anesthesia for tonsillectomy, they learned that in five individuals, so cocainized locally, attempts to swallow iodized oil resulted in its entry into the trachea and bronchi instead of into the esophagus. The authors believe that their observations supply the missing link of evidence in support of the "aspiration" theory.

Interested in the same problem, Iglauer[57] noted blood in the larynx or upper trachea in 19 of 50 patients examined immediately after "local tonsillectomy." Inasmuch as in Ochsner and Nesbit's[56] series the patients had been instructed to swallow after being given the iodized oil, Iglauer observed the course of the lipiodol, slowly introduced into tonsillar fossæ after local tonsillectomy, without giving the 5 patients any instructions; and by fluoroscopic examination found some of the lipiodol in a bronchus in 2 cases, showing that "under ordinary tonsillectomy conditions blood enters the tracheobronchial tract in some, but not all, cases."

RETROSPECTOR'S NOTE.—From these observations it is clear that pulmonary abscesses have been produced in the experimental animal

following the introduction of infected material into the respiratory passages and into the venous circulation. Voluminous data have been presented in favor of, and contrary to, the tenets of both the "aspiration" and "embolic" theories. In the light of our present knowledge of the subject it would seem fair to assume that postoperative abscesses may result from infectious agents which arrive at the lung from the operative site by way of either the tracheobronchial, or the cardiovascular, route.

Irrespective of their controversial significance, these investigations have disclosed many factors, the avoidance of which should point the way to a reduction in the number of cases of postoperative abscess of lung: that is, improper anesthesia; failure to minimize or prevent aspiration of blood and mucus; pathologic processes which interfere with the physiologic mechanism of respiration and consequently favor retention of inspired infectious material; infection (especially fusospirillary-laden lesions) in the upper respiratory passages; infection in the operative field; undue operative trauma, and mass ligation of tissues.

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## RADIOLOGY

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**The Cancer Cell in the Practice of Medicine.**—For many years MacCarty (*Radiology*, 1928, **11**, 379) has sought for earlier histopathologic evidence of malignancy than that commonly known. Often he has seen a suspicious condition, characterized by replacement of normal cells with undifferentiated cells, which has been designated secondary cytoplasia. Since these cells were within the glandular acinus or tubule, a diagnosis of malignancy was not warranted, at that time. Nevertheless, MacCarty believes that all cell conditions which show an analogy to cancer should be radically attacked, for if one waits for the typical histologic criteria of cancer it will be too late.

**Diverticula of the Stomach.**—A case of diverticulum of the posterior wall of the stomach, near the cardia, is reported by Kalbfleisch (*Am. J. Roent. and Rad. Ther.*, 1928, **20**, 218). It produced no gastric or other clinical symptoms, and is therefore supposed to be congenital. The diagnosis was made by roentgen examination, alone. Due to the uncertainty of clinical symptoms, the preoperative diagnosis of diverticula of the stomach rests on the roentgen examination. Kalbfleisch lays stress on the roentgenoscopic examination in the upright and supine positions and especially in the oblique views. Decision as to treatment depends on the symptoms. No definite rules can be laid down. It should be kept in mind, however, that every diverticulum is potentially liable to the development of cancer.

In the same issue (p. 224) BERNSTEIN reports an instance of diverticulum on the lesser curvature one inch below the cardia. The patient, a woman, complained of attacks of pain in the lower right dorsal region accompanied by nausea and vomiting. The cholecystogram was normal and a barium meal revealed the pocket. Its appearance resembled that of perforated ulcer, and, as no mention is made of proof by operation, the reader cannot dismiss this possibility.

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**Radiologic Treatment of Carcinoma of the Cervix.**—As a competitor of surgery, asks GELPI (*Radiology*, 1928, **11**, 403) what has radiation to offer? He answers that radiation by deep therapy does not seem to be well adapted for the purpose and has not come into popular favor, but as an adjunct has a definite field of usefulness, particularly in the control of metastasis extending over large areas. Radiation with radium, however, is especially suitable for the treatment of cervical carcinoma, and the last few years have seen many converts from the ranks of surgeons. As to curability, Clark, of Philadelphia, one of the converts, has compiled statistics showing that radium gives a curability of 43 per cent as against 39.5 per cent by radical operation. The salvage, therefore, is practically equal, but the great difference lies in the primary mortality.

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**Ultraviolet Ray for Secondary Anemia.**—At Iowa State College, JONGEWAARD (*Arch. Physiol. Therap., X-ray and Rad.*, 1928, **9**, 504) has noted that about two-thirds of the girls coming to the clinic have secondary anemia, the hemoglobin ranging from 50 to 70. In all such cases the girls are urged to drink milk, eat largely of food containing iron, go to bed early and be out of doors as much as possible. When deemed necessary, treatment with the ultraviolet ray is given, beginning with an exposure of one minute and increasing until at the end of three or four weeks an exposure of fifteen minutes is applied to each side of the body. Patients thus treated have a marked increase of hemoglobin in from four to eight weeks. Although the work has not been extensive, Jongewaard believes that ultraviolet light may be given first place in the treatment of anemia, with food treatment a close second. A combination of the two seems ideal, since it is evident that sunshine is part of nature's mechanism for promoting the assimilation of iron.

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**Nonmalignant Tumors of the Duodenum.**—GOLDEN (*Am. J. Roentgenol. and Rad. Therap.*, 1928, **20**, 405) has found 17 instances of nonmalignant tumors of the duodenum recorded in the literature and gives details of 2 cases personally observed. The ages of the 19 patients ranged from eleven days to seventy-five years. Most of the tumors were adenomas, a few were myomas, one was a hemangioma and one was a lymphangio-endothelioma. Symptoms suggestive of duodenal ulcer with hemorrhage were noted in many of the cases. In Golden's cases, as in several others, the Roentgen ray examination disclosed a rounded central filling defect in the duodenal bulb. Golden thinks that such a defect associated with a six-hour gastric retention may be considered as evidence of a growth arising in the stomach and prolapsing into the duodenum while the absence of such retention would point to a growth arising in the duodenum itself.

## NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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**Principles of a Rational Penal Code.**—GLUECK (*Ment. Hyg.*, 1929, **13**, 1) reviews the modern trend in investigation and reconstruction of the penal code with special attention to the recommendations of the Italian Penal Code Commission headed by Professor Enrico Ferri and the Fascist Penal Code prepared largely by Signor Rocco. From this consideration he organizes as the basic principle of legal procedure the following: "Society should utilize every scientific instrumentality for self-protection against destructive elements in its midst, with as little interference with the free life of its members as is consistent with such social self protection." Some such basic prinicple, he feels, is required in order to give coherence to the law because the older standards and principles on which laws are based are no longer pertinent to the situation. In modern society it is necessary to discard the old conception of punishment on the basis of just retribution or requittal of wickedness. He styles this principle as "sublimated social vengeance." Also the "expiative theory" must be discarded for the reason that expiation lies within the province of religion and not the province of criminal law. He agrees in principle with Dr. William A. White and Dr. M. Hamblin Smith that our attitude of hatred toward the criminal is a cultivated one in the nature of making the criminal a handy scape goat upon which one can transfer his feeling of his own tendency to sinfulness. He believes that utilitarian justifications of punishment are real and should not be lightly discarded in that the threat of arrest has a deterrent influence and the memory of past punishment has a preventive effect. These should be strengthened rather than weakened by rational modification of the penal code because under the existing system the criminal knows in advance the chances of probation and the length of imprisonment as related to contemplated crimes and he knows that at a certain time he will be given his freedom regardless of improvement or further deterioration. Therefore, the author proposes that we shift the emphasis from the isolated criminal act to the personality of the offender so that "for an offense relatively venial in itself, it is conceivable that a socially dangerous personality may remain incarcerated for life; and for one relatively serious it is likewise conceivable that a person who has profited by institutional or extramural treatment and gives reasonable scientific promise of permanent rehabilitation will be given his liberty after a comparatively short period. The vital element of the possibility of life-long incarceration if the individual is shown by scientific investigation to require it, may reasonably be expected to reinforce the natural deterrent effect of the threat of imprisonment."

Nevertheless, the author believes that punishment is only one of the devices that can be utilized in the correction of crime and that fear is not the only motive of conduct and probably not the most effective motive to appeal to in altering behavior. He calls attention to the trend toward individualization manifested in recent years by the classification of crimes into variations of degree and the "indeterminate sentence" movement, but considers these ineffective and inadequate. He criticizes with justice Ferri's recommendations for a schedule of "conditions of dangerousness" and "conditions of less dangerousness" in that the dangerousness of the criminal is but one feature of his personality make-up and that this principle does not recognize the social justice of constructive rehabilitative work on the basis of individual case study and need. From these considerations he draws his second principle, "The legal and institutional provisions for the protection of society must be based not so much upon the gravity of the particular act for which an offender happens to be tried as upon his personality—that is, upon his dangerousness, his mental and social history, his personal assets, and his responsiveness to penal correctional treatment." He considers that Ferri errs also in drawing up a minute schedule for the estimating of the degrees of dangerousness. He then sets forth four principles of procedure in sentencing criminals: "(1) The treatment (sentence imposing) feature of the procedure must be sharply differentiated from the guilt-finding phase. (2) The decision as to treatment must be made by a board or tribunal specially qualified in the interpretation and evaluation of psychiatric, psychologic, and sociologic data. (3) The treatment must be modifiable in the light of scientific reports of progress. (4) The rights of the individual must be safeguarded against possible arbitrariness or other unlawful action on the part of the treatment tribunal." For these purposes he would turn from criminal law to administrative law for the necessary machinery and considers that certain modifications in substantive law may be expected to result from this basic change in procedure, and these, together with the truly indeterminate sentence provision and improvements in penal correctional practice, would facilitate the work of the treatment body.

## PATHOLOGY AND BACTERIOLOGY

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**The Speed of Appearance of Antibodies.**—The general opinion has been that a considerable time elapses between the introduction of an antigen and the appearance of specific antibodies in the body fluids.

RAMON (*Compt. rend. Soc. de biol.*, 1928, **99**, 1295) after subcutaneous injections of horses with filtrates of formolized cultures of Bacillus pestis was able to demonstrate in less than ten hours the presence in the blood serum of flocculating antibody. The author considers that this demonstration helps to explain the rapid "local immunity" obtained after the use of culture filtrates (Besredka).

**Conjunctivitis of the Newborn.**—The term ophthalmia neonatorum is so closely associated in our minds with the gonococcus that a report by THOMAS (*J. Infect. Dis.*, 1928, **43**, 306) in which the causative agent in 100 cases was an atypical Staphylococcus aureus is of particular interest. The atypical characters were particularly the plemorphism of the cocci and the appearance of metachromasia with the smaller cocci staining Gram negative and the larger positive, seen in direct smear and in cultures, and in reactions with carbohydrates and pathogenicity for animals. Staphylococci identical to those recovered from the eyes were cultured from a large bottle of supposedly sterile olive oil used by the nurses to cleanse the skin of the infants and also from a dish of saturated boric acid solution used to bathe the breasts and nipples of the mothers before the infants were fed. It was, therefore, considered that the infection was probably thus transmitted.

**Undulant Fever.**—Ever since the close relationship between the human, Bacillus melitensis (Bruce, 1887), the bovine, Bacillus abortus (Bang, 1897) and the porcine variety has been recognized, the greatest interest has been aroused in human infections by any member of this group. It is of great importance from the epidemiologic point of view to have detailed information about patients with this infection many of whom have undoubtedly in the past been diagnosed as atypical typhoid fever, influenza or even tuberculosis or malaria or have remained undiagnosed. A recent report on undulant fever in New York State by GILBERT and COLEMAN (*J. Infect. Dis.*, 1928, **43**, 273) brings most important evidence in support of the view that raw cow's milk is a frequent source of the infection in this country. The three types of bacteria are believed to be only varieties of the same microörganism which has become slightly modified by its more recent host and the disease produced should be diagnosed undulant fever. The above report is only one of a long list by American investigators and the European workers are of the same opinion so that it has been suggested by CERRUTI (*J. Trop. Med.*, 1927, **30**, 230) that the name of the microorganism be Brucella melitensis-abortus, Bruce, 1887.

**Intranuclear Inclusions in Yellow Fever.**—TORRES and others (*Comp. rend. Soc. d. biol.*, 1928, **99**, 1344, 1655, 1660, 1669, 1671) have issued a series of short notes upon some observations which they have made upon the tissues of monkeys infected with the virus of yellow fever obtained in Brazil. These authors describe acidophilic intranuclear inclusions arising in the liver cells of the infected animals. These inclusion bodies closely resemble those described by Goopasture and others, in herpes. The inclusion bodies consist of minute granular masses aggregated within the enlarged and ballooned nuclear membrane, within which the chromatin elements appear to have suffered dissolution. Their presence further supports the suggestion that yellow fever is a virus disease.

# HYGIENE AND PUBLIC HEALTH

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**Experimental Transmission of Yellow Fever to Laboratory Animals.**—STOKES, BAUER and HUDSON (*Am. J. Trop. Med.*, 1928, **8**, 103) report the results of experiments which they believe lead to the conclusion that yellow fever in West Africa has been successfully transmitted to monkeys of the species *Macacus rhesus*. Although the strain of the virus with which these experiments were carried out originated from a very mild and clinically almost undiagnosable case in an African, the following evidence supports the conclusion that this virus is that of yellow fever: (1) It was obtained from a case occurring during an epidemic. (2) It is transmissible from man to monkey, as well as from monkey to monkey by injection of blood or serum. (3) It is transmitted by mosquitoes of the species Aedes aegypti. (4) It is filtrable when in the circulating blood. (5) Convalescent serum from a severe case of yellow fever in doses of 0.1 cc. protects monkeys against infection with this virus, while 2 cc. of normal human serum fails to give any protection. (6) The clinical symptoms and the pathologic changes produced by this virus in rhesus monkeys are similar to those in human yellow fever. (7) At the close of the studies with this strain two additional strains of the virus were obtained, both from fatal cases of yellow fever in Europeans, in which the diagnosis was verified by post-mortem findings. Blood from each of these patients injected into rhesus monkeys produced fatal infections. From one of these two patients the disease was also transmitted to monkeys by means of mosquitoes. The clinical course of the disease and the lesions produced by these two strains were similar to those caused by the strain which originated from a mild case and with which most of the work was done.

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**Susceptibility of Eskimos to the Common Cold and a Study of their Natural Immunity to Diphtheria, Scarlet Fever and Bacterial Filtrates.**—HEINBECKER and IRVINE-JONES (*J. Immunol.*, 1928, **15**, 395) state that Eskimos are very susceptible to upper respiratory infections on contact with the outside world. Ordinary bacterial infections rarely occur. Diphtheria and scarlet fever are unknown clinically and in a group of about 50 subjects all were negative to the Dick test and all the adults were also Schick negative. Children up to the age of twelve years were invariably Schick positive. Three serums were found to contain antitoxin both for diphtheria and scarlet fever. It is, therefore, concluded

that the immunity to the disease and the negative skin tests depend upon the presence of antitoxin. This is interpreted as being due to a natural hereditary immunity dependent upon some nonspecific antitoxic mechanism. Skin reactions with filtrates of streptococci isolated from cases of rheumatic fever were mildly positive in a small percentage of cases. Neutralizing antitoxin was demonstrated in all three sera, but it was not invariably present for all three toxins. The Eskimos showed a high percentage of positive reactions when tested with a Staphylococcus aureus filtrate.

## PHYSIOLOGY

PROCEEDINGS OF

### THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH, 1929

**Hemoglobin Maintenance upon Synthetic Diets.**—By D. L. Drabkin and C. S. Waggoner (from the Department of Physiological Chemistry, School of Medicine, University of Pennsylvania, Philadelphia). Five dogs, fed upon the Karr-Cowgill diet[1] for periods of six to eighteen months maintained their hemoglobin at fairly constant normal levels. Sixteen grams (the quantity fed per kilogram body weight) of this synthetic ration were found to contain 0.052 mg. of copper. The copper was determined by the potassium ethyl xanthate method.[2] In the nutritional anemia experiments of Hart and his associates[3] 35 cc. of milk consumed by a rat per day contained 0.01 mg. of copper. For a 50-gm. rat this represented 0.2 mg. copper per kilogram body weight. Therefore, in respect to the ingestion per kilogram of body weight, the amount of copper in the diet fed to our dogs was approximately one-fourth that supplied to Hart's rats on the whole milk (anemia-producing) ration. The hemoglobin maintenance levels of our dogs and the speed of recovery after single large bleedings were not influenced by the addition of $CuSO_4$ to the diet, raising the level of copper fed daily to 1.3 mg. per kilogram of body weight. The method of feeding the ration to which copper had been added was slightly modified to avoid the possibility of incompatibility between the $CuSO_4$ and KI in our salt ration (*i. e.*, formation of insoluble CuI). Furthermore, analysis of the excreta for copper indicated that most of the copper administered was retained by the animal.

It was of interest to determine the source of the copper in our original diet. Surprisingly, analysis of the individual salts in the "salt mixture" proved negative, while the copper content of the commercial casein (the protein component of the diet) and vitavose (used as the source of vitamin B) accounted for the total copper. Modifying the Karr-Cowgill diet by using coagulated egg albumin as the protein and Harris yeast concentrate and dry brewers' yeast as the sources of water-soluble vitamins and with other slight changes we constructed a "copper-free" synthetic diet suitable for rat-feeding experiments. By the addition of $CuSO_4$ to this diet, we had two similar synthetic rations complete in all known dietary essentials and different only in the presence of copper.

When fed *ad libidum* approximately 10 gm. of synthetic diet was consumed per rat per day. In several analyses of 10 to 20 gm. samples of diet by the xanthate method, which is sensitive to 0.01 mg., no copper was found in the ration designated as copper-free. The small quantity of copper added to the copper-free ration in making up the copper-containing diet was quantitatively checked by the xanthate method.

Most of the rats used were of a "skin-parasite-free" strain. They were kept in a special room in individual cages. The possibility of copper contamination of the rats upon the copper-free ration was eliminated. The animals were placed upon the special diets at the age of twenty to twenty-four days. The growth, general appearance and hemoglobin maintenance were normal in the rats on the copper-containing and also in those on the copper-free diet. Five rats upon a whole-milk diet developed a severe anemia. This anemia was promptly cured by placing these rats upon the copper-free synthetic ration. It should be mentioned that diarrhea invariably accompanied milk feeding and in two of the milk rats growth, which had been retarded, was promptly resumed on the copper-free diet.

Further experiments are in progress.

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**The Relation of Climbing Fibers to Purkinje Cells in the Cerebellar Cortex.**—W. H. F. Addison (from the Department of Anatomy, University of Pennsylvania). The nerve fibers entering the gray cortical substance of the cerebellum end as climbing terminals and mossy terminals. The former are associated with the Purkinje cells and the latter with the granule cells. Both were discovered by Ramon y Cajal; in birds in 1888, and in mammals in 1890. The classic type of arrangement of the climbing terminals, as shown by Cajal, is that of a single fiber lying along the Purkinje cell body and main dendrite, and branching at each subdivision of the dendritic arborization. In my study of young cerebella, prepared by the reduced silver methods, I have found many variations.

Frequently two and sometimes three climbing terminals are in relation with one Purkinje cell. These terminals approach the cell body from different directions, and therefore would not appear to be endings of one nerve fiber. Climbing fibers are seen to bifurcate, one branch becoming a climbing terminal, and the other branch continuing straight upward into the molecular layer between the Purkinje cells, quite independent of the latter. This latter variety of fiber terminates at the inner margin of the outer granule layer, sometimes in the form of a small enlargement or *bouton*. A variation of this arrangement is where a climbing terminal is given off from such a straight fiber, above the level of the Purkinje cell bodies, and then appears as a collateral of the straight fiber. Climbing fibers also subdivide in the inner granule layer and the branches diverge toward different Purkinje cells. The study of these young cerebella shows that (1) climbing fibers branch, (2) their branches probably terminate on different Purkinje cells, and

(3) Purkinje cells frequently receive terminals from more than one climbing fiber.

The fundamental nature of the process going on in the cerebellar cortex is associative, and it appears that the climbing fibers play an important part in this, along with the T-shaped axons of the granule cells, the short collaterals of the Purkinje cells, the much-branched axon of the Golgi cells of Type II and the basket terminals of the axons of the basket cells.

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**The Toxicity of Synthalin (Diguanidinodecamethylene).**—W. G. KARR, W. BELK, and O. H. PETTY (from the Graduate School of Medicine, University of Pennsylvania). Synthalin was administered orally (in one animal, neosynthalin, subcutaneously) to dogs maintained on an ordinary house diet. It was given daily in amounts approximating the human therapeutic dose. After a period of two to five weeks the animals vomited, began to refuse their food, and died, with a marked loss of weight, two to three weeks later. The chemical analysis of the blood showed a progressive azotemic nephritis terminating with a marked nitrogen retention. There was only a mild albuminuria until the terminal stage and then accompanied by casts and red blood cells. During this latter stage an appreciable bilirubinemia occurred. Extended autopsy examinations were made and these showed, in particular, marked tubular degeneration of the kidney, especially of the small straight tubules occupying chiefly the deeper part of the cortex. The liver showed a diffuse fatty degeneration.

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**A Specific Conductivity Apparatus for Measuring the Conductivity of Serum Electrolytes.**—F. W. SUNDERMAN (from the Department of Research Medicine, University of Pennsylvania). A specific conductivity bridge and a pipette cell adapted for measuring the conductivity of serum electrolytes agreed with the Kohlrausch method within $\pm 0.6$ per cent in concentrations between 0.1 m. and 1 m. KCl. Somewhat greater deviations were found in more dilute and concentrated solutions. The bridge was constructed for us by the Leeds & Northrup Company and is a modification of the sugar-ash type of bridge.

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